Prodrugs プロドラッグ

A pharmacologically inactive compound that is converted to an active drug by a metabolic biotransformation

代謝反応によって薬理活性を帯びる物質

Utility of Prodrugs

1. Aqueous Solubility 水溶性
2. Absorption and Distribution 吸収・分配
3. Site Specificity 部位特異性
4. Instability 化学的不安定性の解消
5. Prolonged Release 徐放性
6. Toxicity 毒性の回避
7. Poor Patient Acceptability 投薬忌避問題の解消
8. Formulation Problems 製剤上の問題の回避

Types of Prodrugs

I. Carrier-linked prodrug

A compound that contains an active drug **linked to a carrier group that is removed enzymatically**

A. **bipartate** - comprised of one carrier attached to drug

B. **tripartate** - carrier connected to a linker that is connected to drug

C. **mutual** - two, usually synergistic, drugs attached to each other

II. Bioprecursor prodrug

A compound metabolized by molecular modification into a new compound, which is a drug or is metabolized further to a drug - **not just simple cleavage of a group from the prodrug**

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Mechanisms of Prodrug Activation

Carrier-Linked Prodrugs

Hydrolysis — a most common activation reaction.

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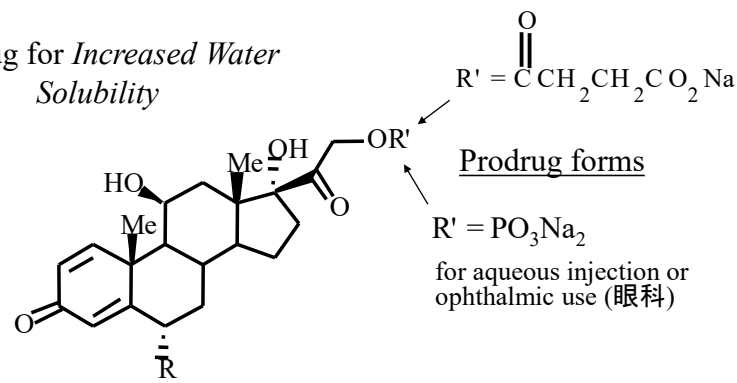
Prodrug for *Increased Water Solubility*



prednisolone (R = R' = H)
methylprednisolone (R = CH_3 , R' = H)

poor water solubility

corticosteroid

The ester is stable enough in water (13 year half-life), but hydrolyzed in vivo with a half-life < 10 minutes.

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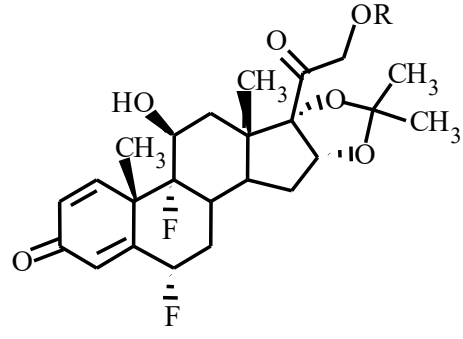
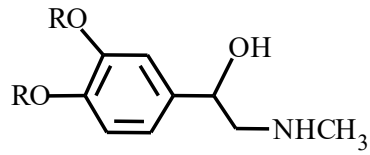
Prodrug for *Improved Absorption* Through Skin



fluocinolone acetonide (R = H)
fluocinonide (R = $COCH_3$)

corticosteroids - inflammation, allergic, pruritic skin conditions

Better absorption into cornea角膜 for the treatment of glaucoma緑内障



dipivefrin (R = Me_3CCO)
epinephrine (R = H)

The cornea has significant esterase activity

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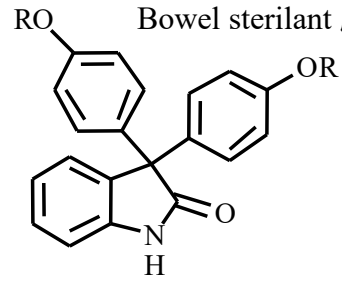
Prodrug for *Site Specificity*



Bowel sterilant 腸管滅菌剤

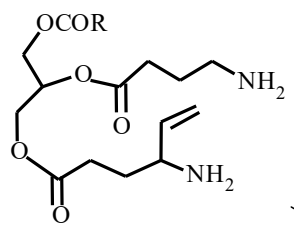
oxyphenisatin (R = H)
(administer rectally直腸)

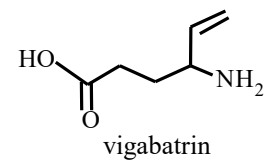
R = Ac (administer orally) hydrolyzed in intestines

Prodrug for *Site Specificity*

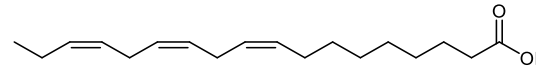
For the passage of the blood-brain barrier

The anticonvulsant drug vigabatrin crosses poorly. A glyceryl lipid (below, R = linolenoyl) containing one GABA ester and one vigabatrin ester was *300 times more potent* in vivo than vigabatrin.





vigabatrin



linolenic acid

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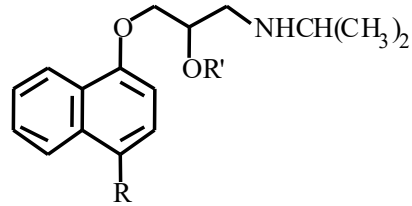
Prodrug for Stability
protection from first-pass effect

Oral administration（経口投与）has lower bioavailability than i.v. injection（静脈注射）.



propanolol (R = R' = H)

Antihypertension (降圧剤)

prodrug R' = $-C(=O)CH_2CH_2COOH$

plasma levels 8 times that with propanolol

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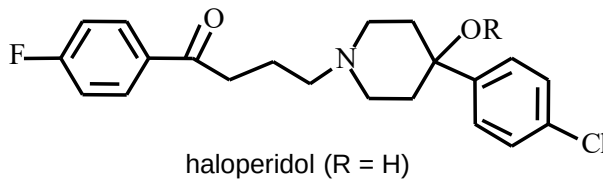
Merits for Slow and Prolonged Release

1. To reduce the number and frequency of doses 投薬頻度の減少
2. To eliminate night time administration 夜間投薬の回避
3. To minimize patient noncompliance 患者の投薬忌避の低減
4. To eliminate peaks and valleys of fast release (relieve strain on cells)

早すぎる薬物濃度変化の緩和（細胞への負担の減少）

5. To reduce toxic levels (毒性の軽減)
6. To reduce GI side effects (消化器系への負担の軽減)

- Long-chain fatty acid esters hydrolyze slowly
- Intramuscular (i.m.) injection（筋肉注射）is used also



haloperidol (R = H)

Sedative/tranquilizer/antipsychotic

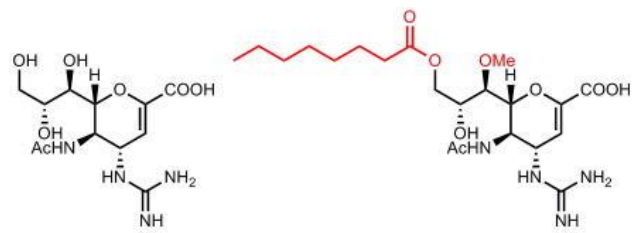
prodrug R = $-C(=O)(CH_2)_8CH_3$

haloperidol decanoate

inject i.m. (筋肉注射)

Antipsychotic activity for about ***1 month***

Flu drug



Zanamivir
(リレンザ)

CS-8958
(イナビル)

taken four times

taken *only one* time

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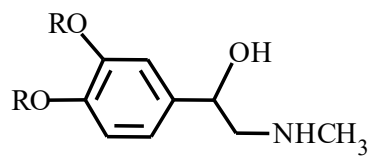
Prodrugs to *Minimize Toxicity*

Many of the prodrugs just discussed also have lowered toxicity.

For example, epinephrine (for glaucoma 緑内障) has ocular and systemic side effects (眼球および全身性副作用) not found in dipivefrin.



dipivefrin (R = Me_3CCO)

epinephrine (R = H)

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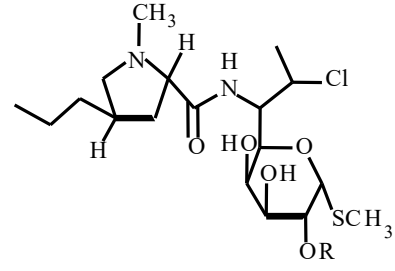
Prodrug to *Increase Patient Acceptance*

The antibacterial drug clindamycin is **bitter** and not well tolerated by children.

Clindamycin palmitate is not bitter.



clindomycin (R = H)

clindomycin palmitate (R = $O(CH_2)_{14}CH_3$)

唾液に不溶 and/or 苦味レセプターへの非結合

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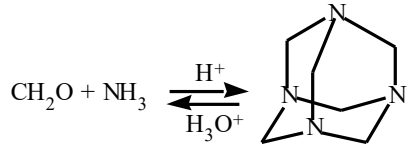
Prodrug to *Eliminate Formulation Problems*

Formaldehyde is a gas with a pungent odor that is used as a disinfectant. Too toxic for direct use.



methenamine

It is a stable solid that decomposes in aqueous acid.

The pH of urine in the bladder is about 4.8, so methenamine is used as a urinary tract antiseptic (尿道の抗菌剤).

Has to be enteric coated (腸溶コーティング) to prevent hydrolysis in the stomach.

Ideal Drug Carriers

1. Protect the drug until it reaches the site of action 作用部位への到達
2. Localize the drug at the site of action 作用部位への局在化
3. Allow for release of drug 薬物の放出
4. Minimize host toxicity 低毒性
5. Are biodegradable, inert, and nonimmunogenic 生分解性かつ非抗原性
6. Are easily prepared and inexpensive 調製容易かつ廉価
7. Are stable in the dosage form 化学的安定性

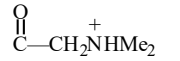
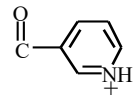
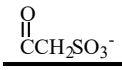
Most common prodrug form is an ester

- esterases are ubiquitous
- can prepare esters with *any degree of hydrophilicity or lipophilicity*
- ester stability *can be controlled* by appropriate electronic and steric manipulations

Prodrugs for Alcohol-Containing Drugs

Ester analogs as prodrugs can affect lipophilicity or hydrophilicity

Drug—OH (alcohols) ⟶ Drug—OX

X	Effect on Water Solubility
	(R = aliphatic or aromatic) decreases (increases lipophilicity)
	increases ($pK_a \sim 8$)
	increases ($pK_a \sim 5$)
	increases ($pK_a \sim 4$)
$PO_3^{=}$ (phosphate ester)	increases ($pK_a \sim 2$ and ~ 6)
	increases ($pK_a \sim 1$)

To accelerate hydrolysis rate:

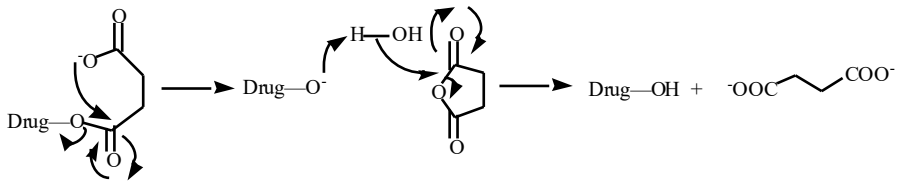
- attach an electron-withdrawing group if a base hydrolysis mechanism is important
- attach an electron-donating group if an acid hydolysis mechanism is important

To slow down hydrolysis rate:

- make sterically-hindered esters
- make long-chain fatty acid esters

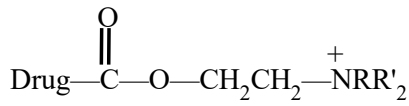
Another Approach to Accelerate Hydrolysis

Intramolecular hydrolysis of succinate esters



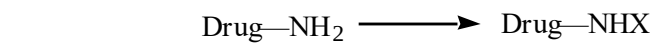
Also, acetals or ketals can be made for rapid hydrolysis in the acidic medium of the GI tract.

In case drug containing carboxylic acids ...

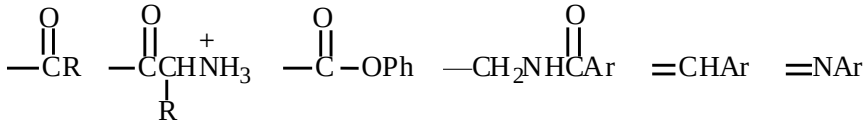


Can vary pK_a by appropriate choice of R and R′

Amine Prodrugs



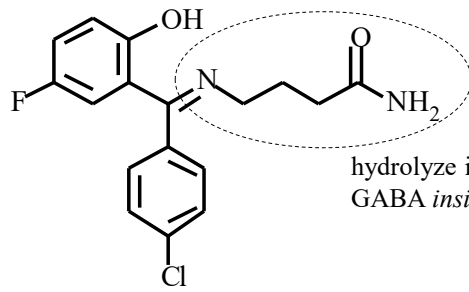
X



Amides are commonly not used because of *stability*

Activated amides (low basicity amines or amino acids) are effective

an example of prodrug for amine drug



hydrolyze imine and amide to GABA *inside* brain

progabide

Anticonvulsant（抗けいれん薬）

Macromolecular Drug Delivery

- A bipartate carrier-linked prodrug in which *the drug is attached to a macromolecule*, such as a synthetic polymer, protein, lectin, antibody, cell, etc.

  ポリマーをキャリアとするbipartate prodrug

- Absorption/distribution depends on the *physicochemical properties of macromolecular carrier*, not of the drug. Therefore, attain better targeting.

  薬物動態はポリマーの物理化学的性質で決まるので，ターゲッティングに有利

- Minimize interactions with other tissues or enzymes. Fewer metabolic problems; increased therapeutic index.

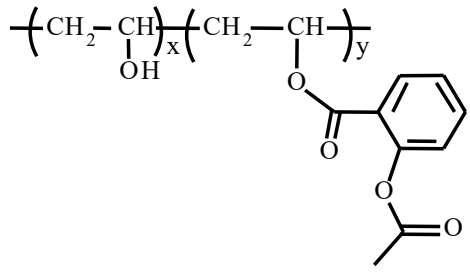
  目的臓器以外での作用を最小限にできる

Problems

- low degree of absorption 低吸収性
- needs intravenous injection 静脈注射などの必要性
- shows antigenicity 抗原性

Macromolecular Drug Carriers

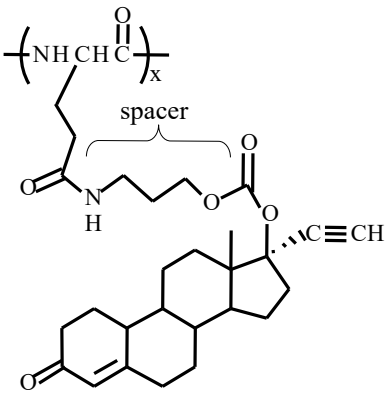
Synthetic polymers



Aspirin linked to poly(vinyl alcohol) has about the same potency as aspirin, but less toxic.

Poly(α-Amino Acid) Carriers

poly(*L*-glutamine)



norethindrone – contraceptive 避妊薬

Slow release over *nine months* in rats

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Tripartate Drugs
(Self-immolative自壊性Prodrugs)

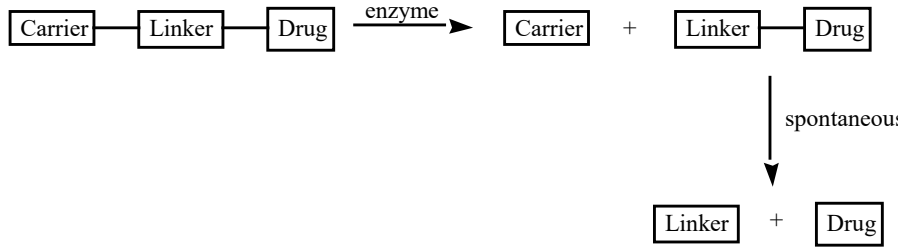
- A bipartate prodrug may be ineffective because **the linkage is too labile or too stable.**

  bipartate prodrug が安定過ぎ／不安定すぎで効かないというケースがある

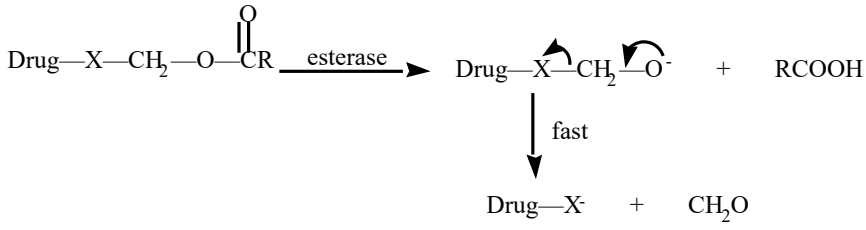
- In a tripartate prodrug, the carrier is not attached to the drug; rather, to the linker.

  linkerを導入することで，加水分解サイトをdrugから離す

Tripartate Prodrugs



Typical Approach



Tripartate Prodrugs of Ampicillin

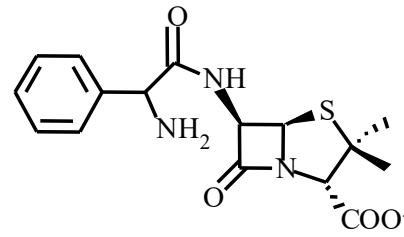
Poor oral absorption (40%) 低吸収性

Excess antibiotic may destroy important intestinal bacteria used in digestion and for biosynthesis of cofactors.

過剰使用により腸内細菌が死滅する

Also, more rapid onset of resistance.

また，耐性菌の出現も加速する



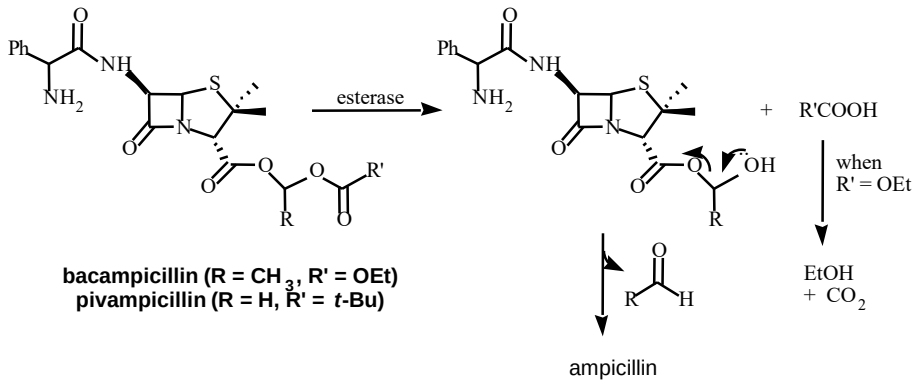
ampicillin

Antibacterial (抗生物質)

Various esters made were too stable in humans（エステルだと安定過ぎ）

- thought the thiazolidine ring **sterically hindered** the esterase.（立体障害）

Tripartate Prodrugs of Ampicillin

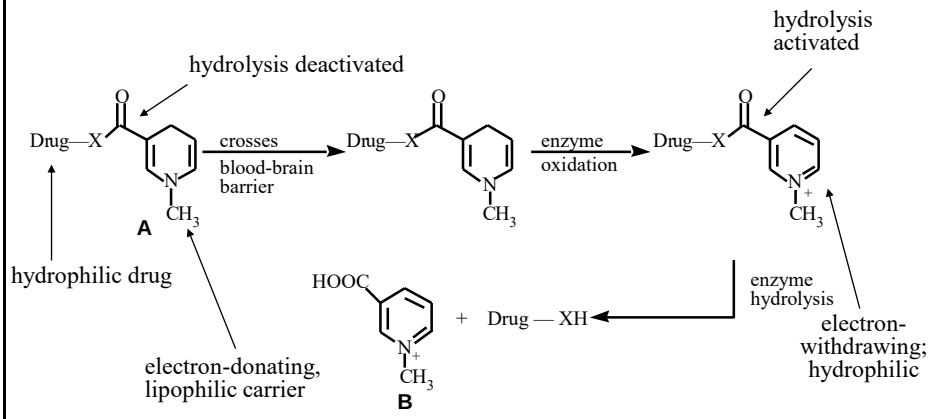


bacampicillin (R = CH_3, R' = OEt)
pivampicillin (R = H, R' = *t*-Bu)

98-99% absorbed

Ampicillin is released in < 15 minutes

Reversible redox drug delivery system to the CNS 中枢神経系



Passive diffusion of **A** into the brain; active transport of **B** out of the brain

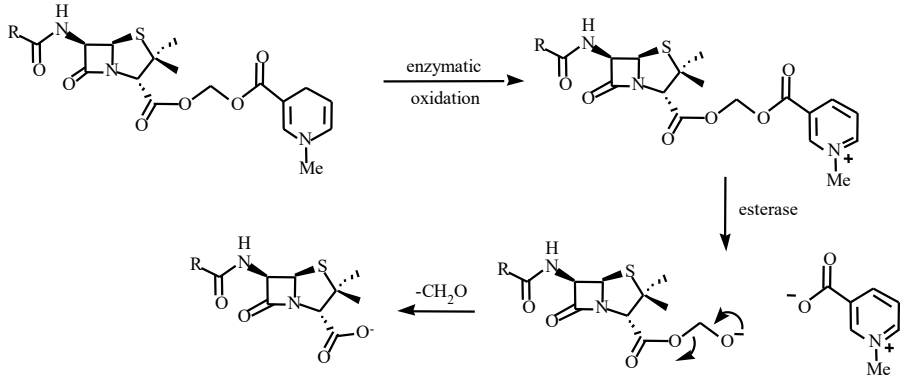
XH of the drug is NH_2, OH, or COOH

If oxidation occurs before it gets into the brain, it cannot cross the blood-brain barrier.

Example of Redox Drug Delivery

Antibody generation *in the brain* is not significant.

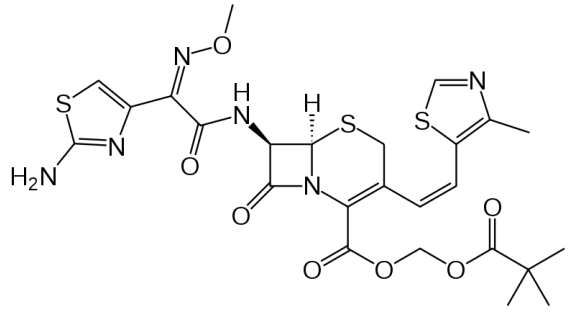
β-Lactams are too hydrophilic to cross the blood-brain barrier effectively.

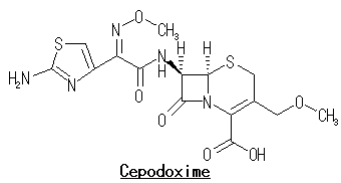


High concentrations of β-lactams *delivered into brain*.

Medicine 薬

Antibiotic 抗生物質

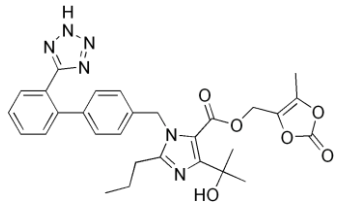




Cepodoxime

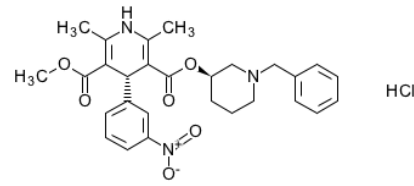
tripartite prodrug!!

Medicine 薬



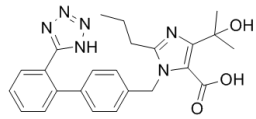
angiotensin II receptor antagonist
アンジオテンシンII受容体 拮抗

also prodrug!!



calcium channel blocker
カルシウム拮抗

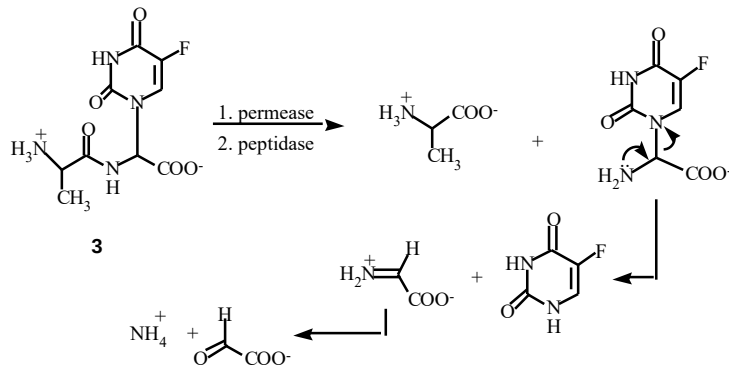
(こちらはprodrugではない)



(active species)

Tripartate Prodrug for *Delivery of Antibacterials*

Permeases are bacterial transport proteins for uptake of peptides.



3

Types of Prodrugs

I. Carrier-linked prodrug

A compound that contains an active drug **linked to a carrier group that is removed enzymatically**

A. **bipartate** - comprised of one carrier attached to drug

B. **tripartate** - carrier connected to a linker that is connected to drug

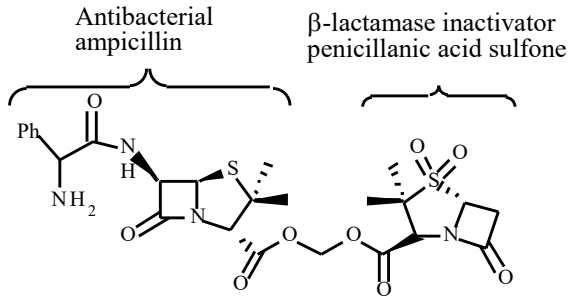
C. **mutual** - two, usually synergistic, drugs attached to each other

II. Bioprecursor prodrug

A compound metabolized by molecular modification into a new compound, which is a drug or is metabolized further to a drug - **not just simple cleavage of a group from the prodrug**

Mutual Prodrugs (or codrug　相互プロドラッグ)

A bipartate or tripartate prodrug in which the carrier is a *synergistic drug* with the drug to which it is linked.



sultamicillin

Hydrolysis gives 1:1:1 ampicillin : penicillanic acid sulfone : formaldehyde

Ideal Mutual Prodrugs

- Well absorbed 良吸収性
- Both components are released together and quantitatively after absorption 吸収後の薬物放出が高効率
- Maximal effect of the combination of the two drugs occurs at 1:1 ratio ２つの薬物の存在比が１:１のときに最大効率
- Distribution/elimination of components are similar 分布・排出が同じ速度で起こる

Types of Prodrugs

I. Carrier-linked prodrug

A compound that contains an active drug **linked to a carrier group that is removed enzymatically**

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Bioprecursor Prodrugs

Carrier-linked prodrugs largely use hydrolytic activation

Bioprecursor drugs mostly use *oxidative or reductive activation*

---

cf. Protecting group analogy for the concept of prodrugs

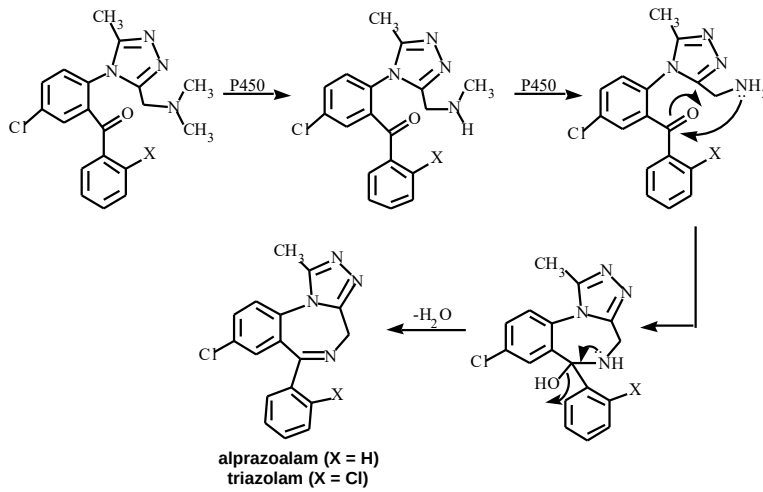
A. $RCO_2H \xrightarrow[HCl,\ \Delta]{EtOH} RCO_2Et \xrightarrow[\text{on R}]{\text{reaction}} R'CO_2Et \xrightarrow[\Delta]{H_3O^+} R'CO_2H$ analogous to carrier-linked

B. $RCH{=}CH_2 \xrightarrow[\text{on R}]{\text{reaction}} R'CH{=}CH_2 \xrightarrow[2.\ H_2O_2]{1.\ O_3} R'CO_2H$ analogous to bioprecursor

Oxidative Activation

N-Dealkylation

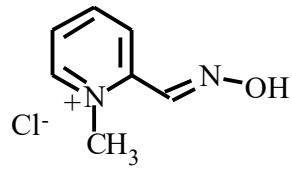
Sedative 鎮靜劑



N-Oxidation

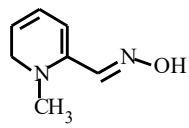
Pralidoxime chloride is an antidote for nerve poisons
神経毒の解毒剤.

It reacts with acetylcholinesterase that has been inactivated by organophosphorus toxins.
有機リン系毒薬（eg サリン）によるアセチルコリンエステラーゼ阻害からの酵素再生



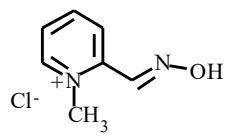
pralidoxime chloride

To increase the permeability of pralidoxime into the CNS, the pyridinium ring was reduced



Hydrophobic, crosses the blood-brain barrier

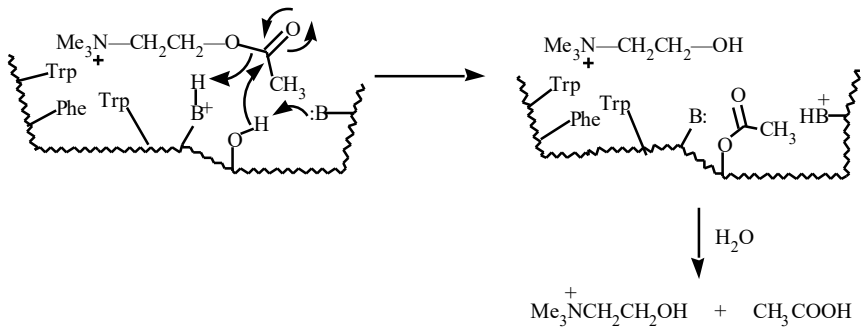
oxidation into brain



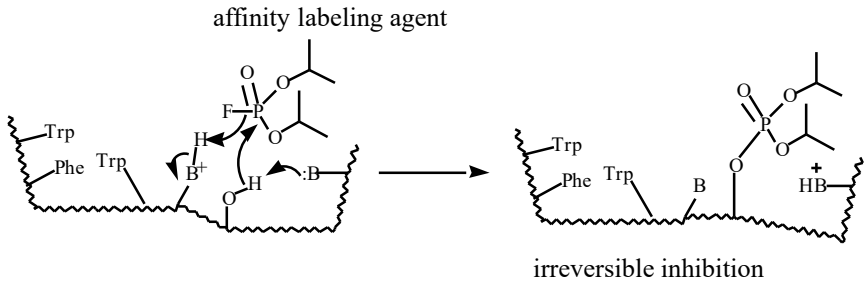
efflux from brain does not occur

pralidoxime chloride

Mechanism of Acetylcholinesterase

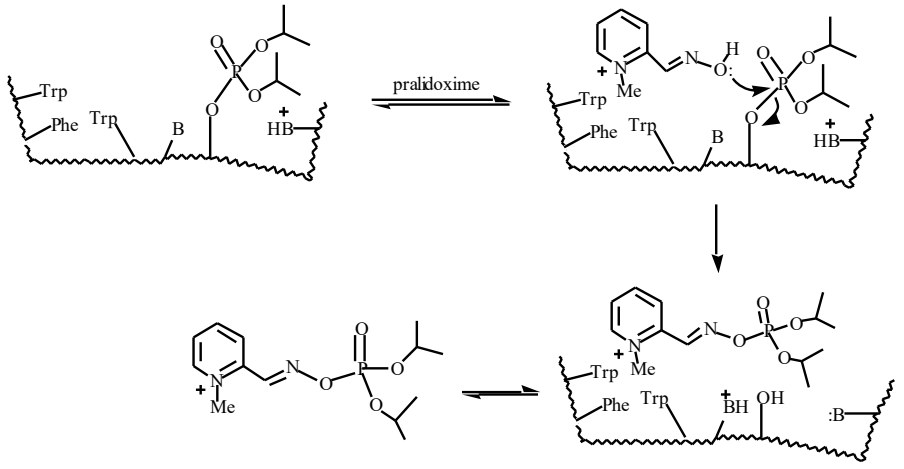


Inactivation of Acetylcholinesterase by Diisopropyl Phosphorofluoridate



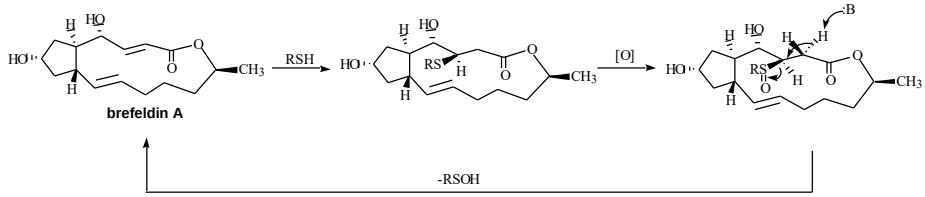
Inactivation prevents degradation of the excitatory neurotransmitter acetylcholine. Accumulation of acetylcholine causes muscle cells in airways to contract and secrete mucous (粘液分泌), then muscles become paralyzed（麻痺）.

Reactivation of Inactivated Acetylcholinesterase by Pralidoxime



S-Oxidation

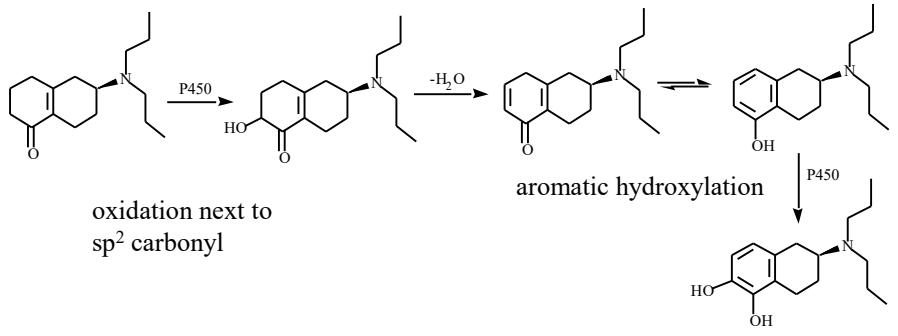
Poor oral bioavailability of brefeldin A. Converted to Michael addition sulfide prodrug. *S*-Oxidation and elimination gives brefeldin A.



antitumor, antiviral agent
抗腫瘍・抗ウィルス

Aromatic Hydroxylation

Cyclohexenones as prodrugs for catechols



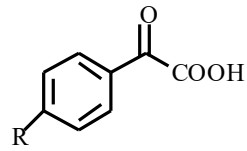
oxidation next to
sp^2 carbonyl

Transamination

- Stimulation of pyruvate dehydrogenase results in a change of myocardial metabolism from fatty acid to glucose utilization.
- Glucose metabolism requires less O_2 consumption.
- Therefore, utilization of glucose metabolism would be beneficial to patients with ischemic heart disease (arterial blood flow blocked; less O_2 available).

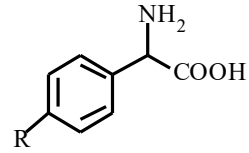
Transamination-targeted bioprecursor

Arylglyoxylic acids (**X**) stimulate pyruvate dehydrogenase, but have a short duration of action.



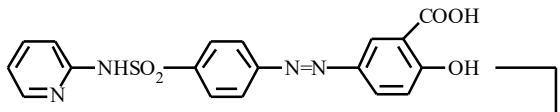
X

Oxfenicine (**Y**, R = OH) is actively transported and is transaminated (a PLP aminotransferase) in the heart to **Y** (R = OH).



oxfenicine (R = OH)
Y

Reductive Activation
Azo Reduction

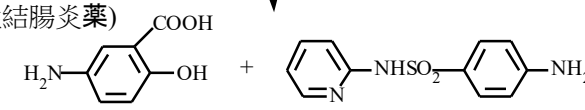


sulfasalazine

ulcerative colitis (潰瘍性結腸炎**藥**)

For inflammatory bowel disease

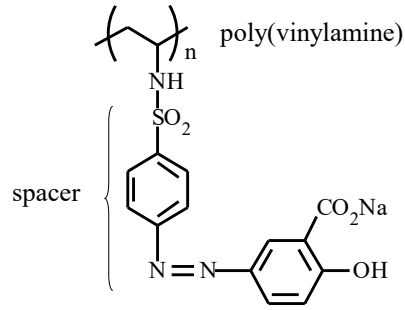
Anaerobic cleavage by bacteria in lower bowel



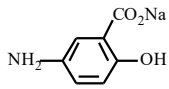
sulfapyridine

Causes side effects

To prevent side effect by sulfapyridine a macromolecular delivery system was developed.



Not absorbed or metabolized in small intestine.



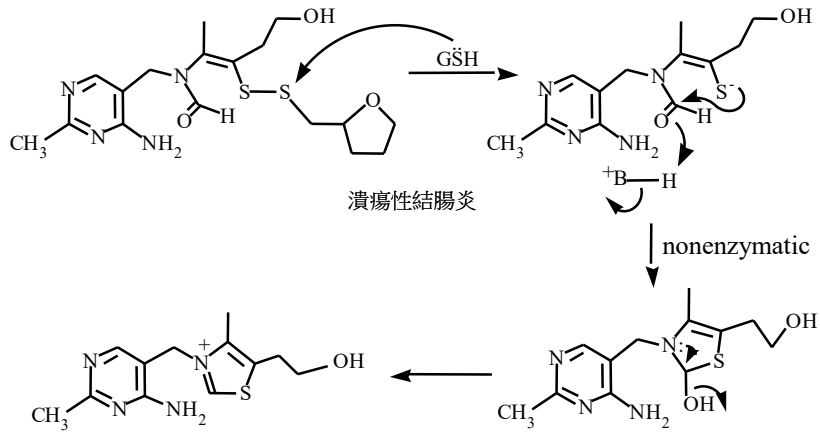
Released by reduction at the disease site.

Sulfapyridine is not released (still attached to polymer).

More potent than sulfasalazine.

Disulfide Reduction

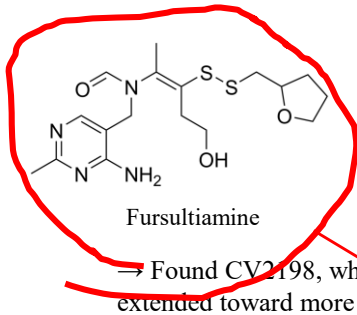
To increase the lipophilicity of thiamin for absorption into the CNS.



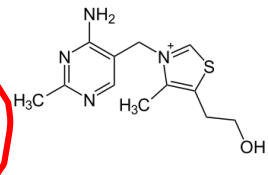
poorly absorbed into CNS

Earlier 1970's, Takeda Pharmaceutical Co. Ltd. started seeking lead compounds for antihypertensive

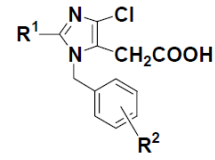
Method: Screening "Fursultiamine (VB1 precursor)" metabolite compounds for diuretic activity (利尿作用), because diuretics are known to lower blood pressure.
[cf. 3. Drug metabolism studies]



Fursultiamine



Vitamin B1

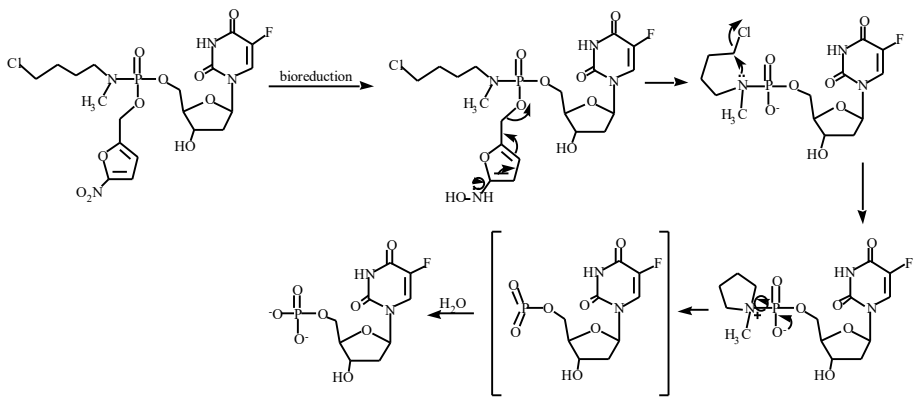


CV2198 (R_1 = Ph, R_2 = H)

→ Found CV2198, which showed ARB activity. Takeda had extended toward more effective ARB by animal test using spontaneously hypertensive mice.

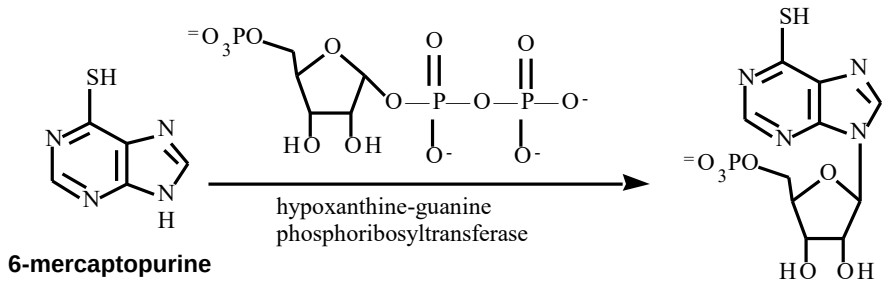
Bioprecursor!!

Nitro Reduction



Mechanism-based inactivator of thymidylate synthase

Nucleotide Activation

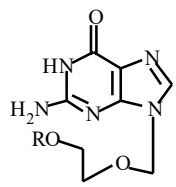


6-mercaptopurine

Anti-leukemia drug 抗白血病薬

Inhibits several enzymes in the purine nucleotide biosynthesis pathway.

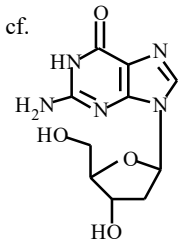
Phosphorylation Activation



acyclovir (R = H)

Antiviral 抗ウィルス薬

cf.



2′-deoxyguanosine

Uninfected cells do not phosphorylate acyclovir (selective toxicity)

↓ *viral* thymidine kinase

$R = PO_3^{=}$

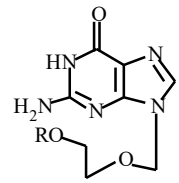
↓ *viral* guanylate kinase

$R = P_2O_6^{-3}$

↓ *viral* phosphoglycerate kinase

$R = P_3O_9^{-4}$

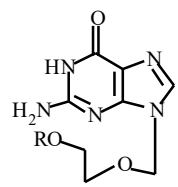
- Acyclovir triphosphate is a substrate for *viral* α-DNA polymerase but not for normal α-DNA polymerase
- Incorporation into viral DNA leads to a dead-end complex (not active). Disrupts viral replication cycle and destroys the virus.
- Even if the triphosphate of acyclovir were released, it is too polar to be taken up by normal cells.
- High selective toxicity



acyclovir (R = H)

Resistance to Acyclovir

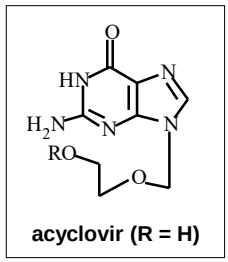
- Modification of thymidine kinase
- Change in substrate specificity for thymidine kinase
- Altered viral α-DNA polymerase



acyclovir (R = H)

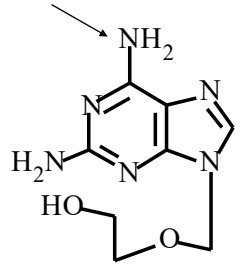
Only 15-20% of acyclovir is absorbed

Therefore, prodrugs have been designed to increase oral absorption.



acyclovir (R = H)

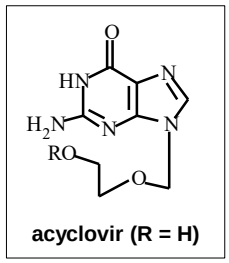
Hydrolyzes here



Prodrug for acyclovir

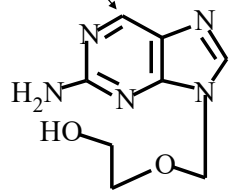
adenosine deaminase

acyclovir



acyclovir (R = H)

Hydroxylates here

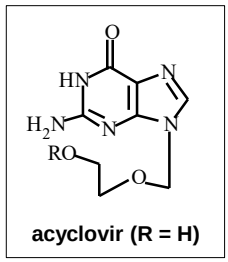


xanthine oxidase

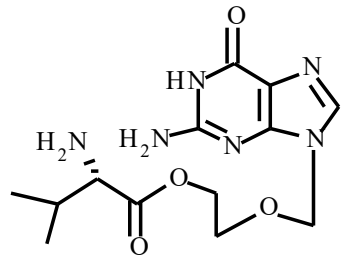
acyclovir

This prodrug is 18 times more water soluble than acyclovir.

A bipartate carrier-linked prodrug of acyclovir, the *L*-valyl ester of acyclovir, has 3-5 fold higher oral bioavailability with the same safety profile.

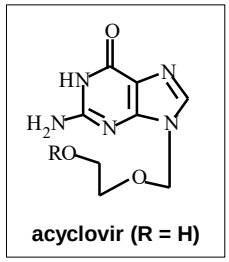


acyclovir (R = H)

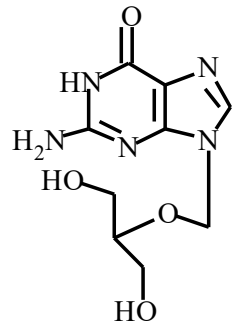


valaciclovir

An analog of acyclovir whose structure is even closer to that of 2′-deoxyguanosine is ganciclovir.



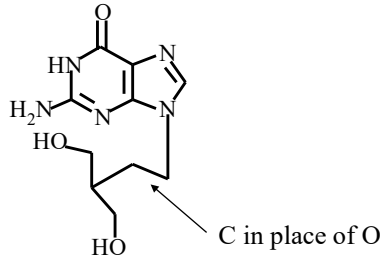
acyclovir (R = H)



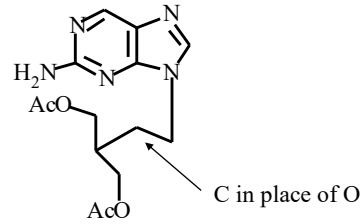
ganciclovir

More potent than acyclovir against human cytomegalovirus.

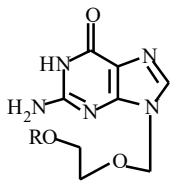
Two carbon isosteres of ganciclovir are available.



penciclovir



famciclovir



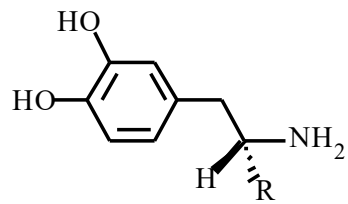
acyclovir (R = H)

- Better oral absorption than penciclovir
- Converted to penciclovir rapidly

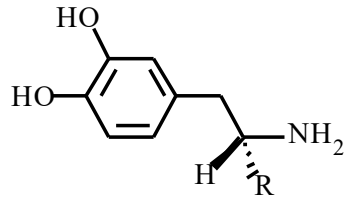
Decarboxylation Activation

In Parkinson's (パーキンソン病) there is a loss of dopaminergic neurons（ドーパミン産生ニューロン）and a low dopamine concentration.

Dopamine treatment does not work because it cannot cross blood-brain barrier, but there is an *active transport system* for *L*-dopa.



dopamine (R= H)
***L*-dopa (R= COOH)**



levodopa (R = COOH)

After crossing blood-brain barrier

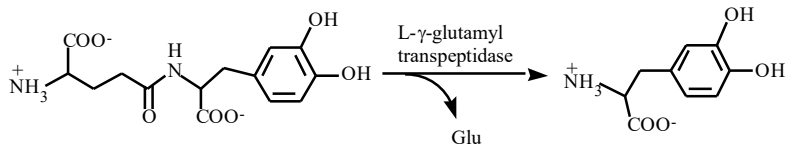
L-aromatic amino acid decarboxylase (PLP)

dopamine (R = H)

Does not reverse the disease, only slows progression.

Selective Delivery of Dopamine to Kidneys

Dopamine can be used for selective renal vasodilation（腎臓の血管拡張）

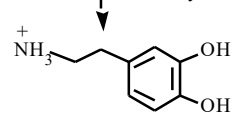


L-γ-glutamyl-*L*-dopa

L-dopa

L-aromatic amino acid decarboxylase

Dopamine accumulates in the kidneys because of *high concentrations* of *L*-γ-glutamyltranspeptidase and *L*-aromatic amino acid decarboxylase there.



Dopamine

Example of a carrier-linked prodrug of a bioprecursor prodrug for dopamine.

Mechanisms of Drug Resistance
薬物耐性

1. Altered drug uptake - exclusion of drug from site of action by blocking uptake of drug - altered membrane with more + or – charges 薬物の取り込みの減少

2. Overproduction of the target enzyme - gene induced 酵素の過剰発現

3. Altered target enzyme (mutation of amino acid residues at the active site) - drug binds poorly to altered form of the enzyme 酵素の変異

4. Production of a drug-destroying enzyme - a new enzyme is formed that destroys the drug 薬物分解酵素の生産

Mechanisms of Drug Resistance (cont'd)

5. Deletion of a prodrug-activating enzyme - the enzyme needed to activate a prodrug is missing プロドラッグ活性化酵素の消失

6. Overproduction of the substrate for the target enzyme - blocks inhibitor binding 標的酵素の基質の過剰生産

7. New metabolic pathway for formation of the product of the target enzyme - bypass effect of inhibiting the enzyme 別な酵素の反応による物質生産

8. Efflux pump - protein that transports molecules out of the cell

薬物を細胞から排出するポンプの作動

Penicillin Resistance

β-Lactamase production - hydrolyzes β-lactam ring

Also, transpeptidase becomes less susceptible to acylation.

Membrane permeability is modified.