Prodrugs and Soft Drugs

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Prodrugs, Soft Drugs and Targeted Drugs

Prodrugs are inactive (less active) drug analogs with better pharmacokinetic properties (e.g. oral bioavailability, BBB penetration).

Soft drugs (antedrugs) are drugs that are readily degraded to inactive analogs, e.g. to prevent or reduce systemic activity.

Targeted drugs are drugs or prodrugs which exert their biological action only in certain cells or organs (e.g. omeprazole, aciclovir).
Why Prodrugs?

Drug is not (sufficiently) bioavailable (most prodrug concepts)
Drug does not permeate the blood-brain barrier (dopamine, GABA)
Drug has poor properties (solubility, taste)
Drug has no (sufficient) chemical stability (active principles of acetylsalicylic acid, isoniazid, omeprazole, clopidogrel)
Drug has no (sufficient) organ or cell specificity (sulfamethoxazole, capecitabine, aciclovir)

Introduction

L: Liberation
A: Absorption
D: Distribution
M: Metabolism
E: Elimination
T: Toxicity

Reasons for Clinical Failure
Liberation: Better Soluble Drug Derivatives

Metamizole (e.g. Novalgin®)

Fosfluconazole

Fosamprenavir

The Doctrine of Signatures: „Nature helps Mankind“

Willow tree – Roots in Water – Feet in Water - Common Cold
Aspirin®, a Prodrug? (Felix Hoffmann, 1897)

Prodrugs: Esters

- clofibrate, $R = \text{Et}$
- clofibrate acid, $R = \text{H}$
- chloramphenicol, $R = \text{H}$ (very bitter taste)
- tasteless prodrug
  $R = \text{CO(CH}_2\text{)}_{14}\text{CH}_3$
The Serendipitous Discovery of the Pill


Prodrugs: Lactones

HMG-CoA reductase

HMG-CoA

mevalonic acid

cholesterol

active metabolite

lovastatin

Birch reduction

enol ether cleavage

metabolic cleavage

gastric juice

Norethynodrel (Enovid, Searle)

Norethindrone

Mestranol

Ethinylestradiol

Prodrugs: Lactones

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Phenacetin, a Pro-Prodrug

N-hydroxy- and quinone metabolites (hepato- and nephrotoxic)

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\begin{align*}
\text{Phenacetin} & \xrightarrow{\text{P450}} \text{Paracetamol (acetaminophen; active metabolite)} \\
\text{Phenetidin} & \xrightarrow{\text{toxification}} \text{(methemoglobin formation)}
\end{align*}
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Mode of Action of Acetaminophen

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\begin{align*}
\text{Paracetamol (acetaminophen)} & \xrightarrow{\text{toxification}} \text{Arachidonic acid} \\
\text{p-Amino-phenol} & \xrightarrow{\text{fatty acid amidohydrolase (FAAH)}} \text{N-arachidonoyl phenolamine, a potent TRPV1 (transient receptor potential vanilloid 1, vanilloid receptor) agonist, } pEC_{50} = 7.80 \text{ (about 16 nM), binds also to the cannabinoid CB}_1 \text{ receptor and inhibits cellular anandamide uptake.}
\end{align*}
\]
Clopidogrel, Mode of Action

- **Oxidation (15%, activation)**
  - CYP 3A4
  - **Plavix®, Iscover®** (Sanofi-Aventis, BMS)
  - Worldwide net sales 2005: about 6 bio US-

- **Hydrolysis (85%, deactivation)**
  - Active metabolite, irreversibly reacts in the liver with platelet P2Y12 (ADP) receptors
  - Activation by CYP2C19 (absent in 30% Caucasians)


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Mode of Action of Isoniazid

Isoniazid and its analogs considered to be prodrugs of antimetabolites of nicotinic acid

- **Isoniazid**
  - KatG
- InH

**Soft Drugs: Metabolically Labile Esters**

- **Succinylcholine**, an acetylcholine analog; ester cleavage produces inactive choline
- **Esmolol**, a soft β-blocker; ester cleavage produces weakly active acid
- **Articaine**, a soft local anesthetic
- **Atropin**
  - $R = \text{CH}_2\text{OH}$
  - $R = \text{COOR}$, ester bioisoster, cleavage yields inactive acid

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**Organ- and Cell-Specific Drug Delivery**

**Organ Specificity**, mediated by
- physicochemical properties (lipophilicity)
- transporters (uptake, efflux)
- metabolism only or preferentially in target organ

**Cell Specificity**, mediated by
- cellular metabolism
- intracellular degradation

**Other mechanisms** of organ-specific action
- local application (eye, skin, lung, spinal cord)
- antibody conjugates
- target localisation
- target type (e.g. microorganism targets)
**Lipophilicity and Blood-Brain Barrier**

**Polar Compounds**
- Epinephrine
- Dopamine

**Lipophilic Compounds**
- Amphetamine (speed)
- MDMA (Ecstasy, XTC)

**Intermediate Lipophilicity**
- Ephedrine

**Organ-Specific Delivery: Parkinson’s Disease**

Caused by degeneration of dopamine-producing cells in Substantia nigra.
A Rational Therapy of Parkinson's Disease

- **healthy**
  - ACh: +
  - dopamine: +

- **sick**
  - ACh: ↓
  - dopamine: ↑

**Problems**
- dopamine is not bio-available, peripheral side effects, MAO

**Therapy**
- oral L-DOPA, peripheral DOPA decarboxylase blocker, central MAO blocker

Integrated Optimisation of Drug Therapy
Dopamine Substitution in Parkinson's Disease

- L-dopa as dopamine prodrug
- Brain: dopamine
- Periphery: inactive metabolites
- Benserazide
- (R)-(-)-Selegiline
Avoidance of CNS Effects by Active Efflux

Terfenadine, $R = \text{CH}_3$
lipophilic H$_1$ antagonist
(no sedative side effect,
due to active elimination
by drug transporter)

Fexofenadine, $R = \text{COOH}$
active terfenadine metabolite

Loperamide
antidiarrhoicum
(opiate agonist without
CNS activity)

Soft Drugs: Corticosteroid Esters

fluticasone propionate
(Flonase; Advair, GSK)
(inhalation; topically active
in asthma treatment)

first pass (99%)

R. E. Pearce et al., Drug Metab. Dispos. 34, 1035-1040 (2006)
Soft Drugs: Corticosteroid Esters

fluocortolone

(topically and systemically active)

oxidation

esther formation

(topically and systemically inactive)

(topically active, but systemically inactive, due to rapid hydrolysis after dermal absorption)

Kidney-Selective Vasodilation

γ-glutamyl-dopa

γ-glutamyl transpeptidase

L-amino acid decarboxylase

γ-glutamyl derivatives of amino acids and peptides accumulate in the kidney, where they undergo selective metabolic activation

Kidney-Selective Release of the Antiinfective Sulfonamide Sulfamethoxazole

1) N-acylamino acid deacylase
2) γ-glutamyl transpeptidase

both enzymes are present in high concentration in the kidney


Colon-Selective Delivery of Corticosteroids in Inflammatory Bowel Disease

R = H, Dexamethasone
oral dose almost exclusively absorbed in the intestine, only about 1% reach the cecum

R = glucose, Dexamethasone-21β-D-glucoside
cleaved by the colonic microflora, about 60% of the free steroid reach the cecum

Antiviral Prodrugs are Trojan Horses

1) monophosphorylation by viral thymidine kinase

2) phosphorylation by cellular kinase

DNA polymerase inhibition (chain termination)

Valaciclovir, a pro-drug of aciclovir

Tumor Cell-Specific Trojan Horses

Capcitabine, orally active prodrug, tumour-specific activation by a cascade of enzymes:

1) carboxypeptidase cleavage (liver)
2) cytidine deaminase (liver, tumours)
3) thymidine phosphorylase (tumours)

5-fluorouracil

5-F-2’-desoxy-uridylate

(thymidylate synthase inhibitor)
Promising Prodrugs Are Expensive

In 2012, Gilead Sciences was going to pay 11 billion US-$ for Pharmasset, a company with only 82 employees and no product in the market. However, they have PSI 7977 in early clinical phase III studies.

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\text{PSI-7977}
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tested in combination with Ribavirin, as the first oral treatment for hepatitis C.


Why Drugs Are So Expensive

In January 2012, Bristol-Myers Squibb acquired Inhibitex for $ 2.5 billion, to get access to an NS5b inhibitor for the potential treatment of hepatitis C. Because of a heart failure-associated death case in one patient and hospitalization of eight others, phase II clinical trials were terminated August 01, 2012.

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\text{BMS-986094}
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Omeprazole: A Cell-Specific Anti-Ulcer Agent

1966: Local anesthetics reduce gastric secretion (Hässle)
1966-1972: First lead
1972-1979: New lead pyridyl-acetamide (from screening of antiviral compounds)
Active analogs; metabolite with higher antisecretory activity

Tox study: picoprazole group, placebo group
picoprazole group, breeding dog Fabian
vasculitis

Omeprazole Analog: Toxic or not Toxic?

Picoprazole, 1976 preclinical candidate
Drug Activation in Acid-Producing Cells - The Serendipitous Discovery of a Targeted Drug

Omeprazole Activation in Acid-Producing Cells

Distribution of radio-labelled omeprazole, one minute after i.v. injection, rat

sixteen hours after i.v. injection, rat

courtesy of Dr. K. Andersson, AstraZeneca, Sweden
References


