Pharmacokinetics

Distribution

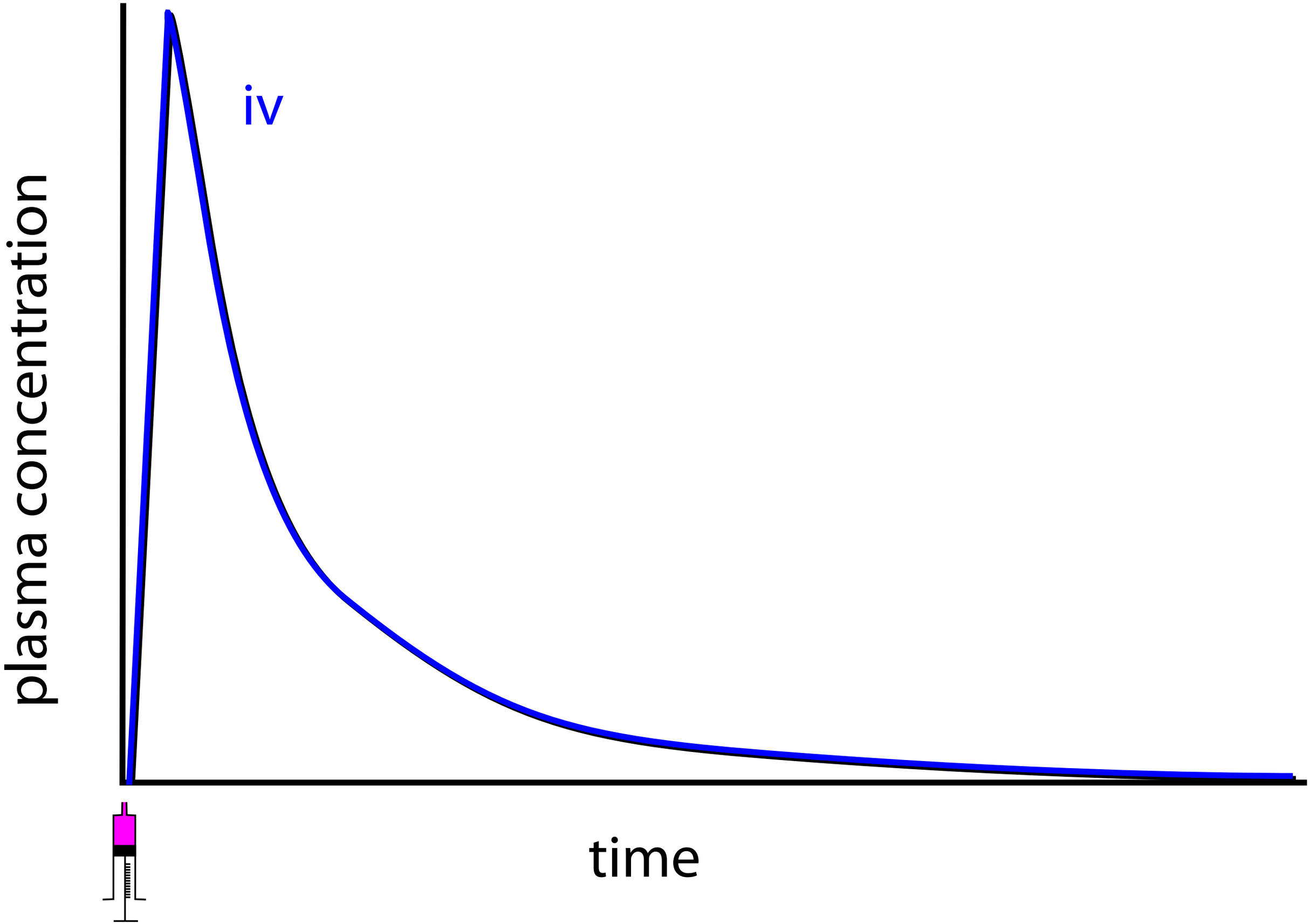
by the end of this lecture you should be able to

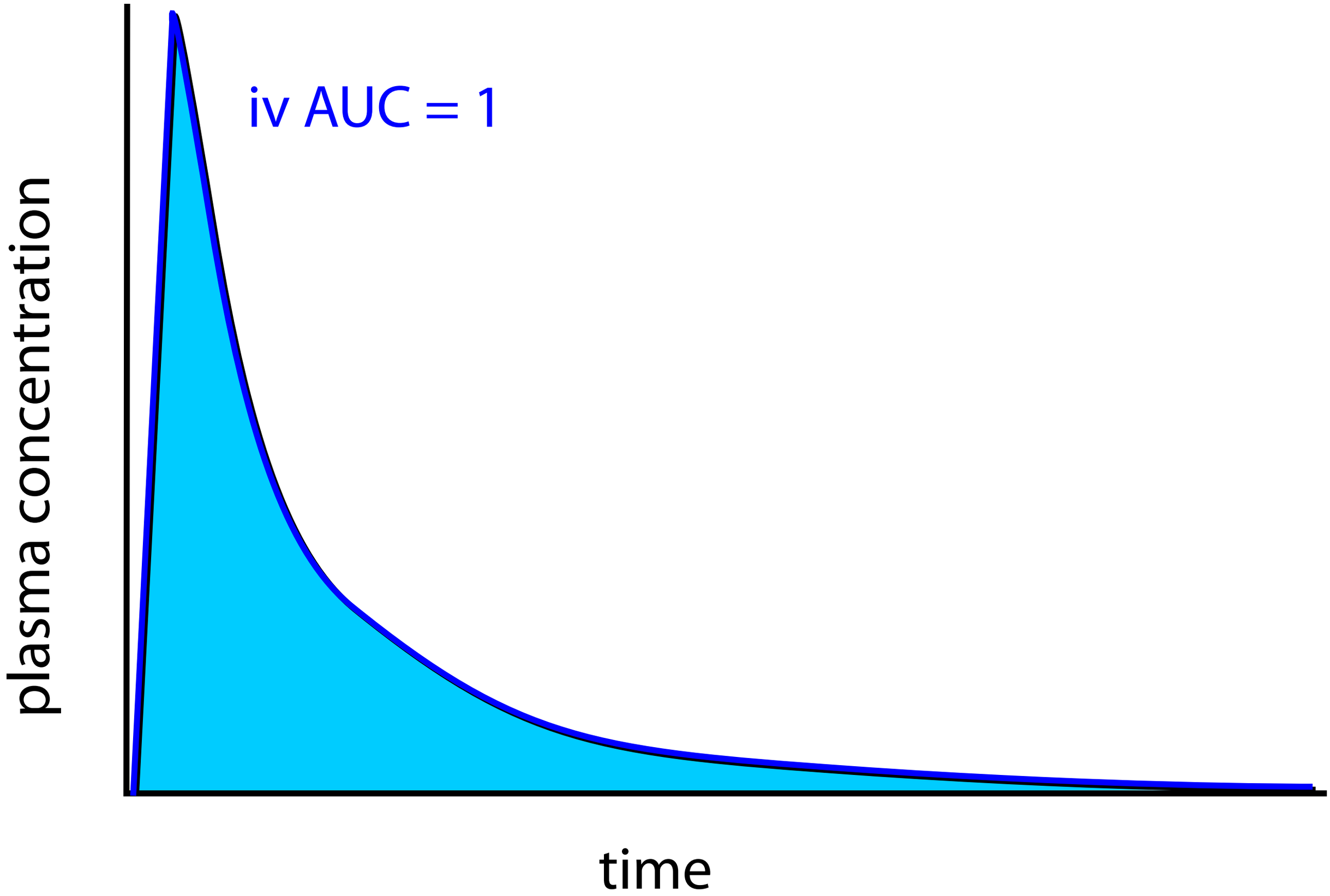
- use your knowledge of PKs to ensure that a drug gets to its intended site of action

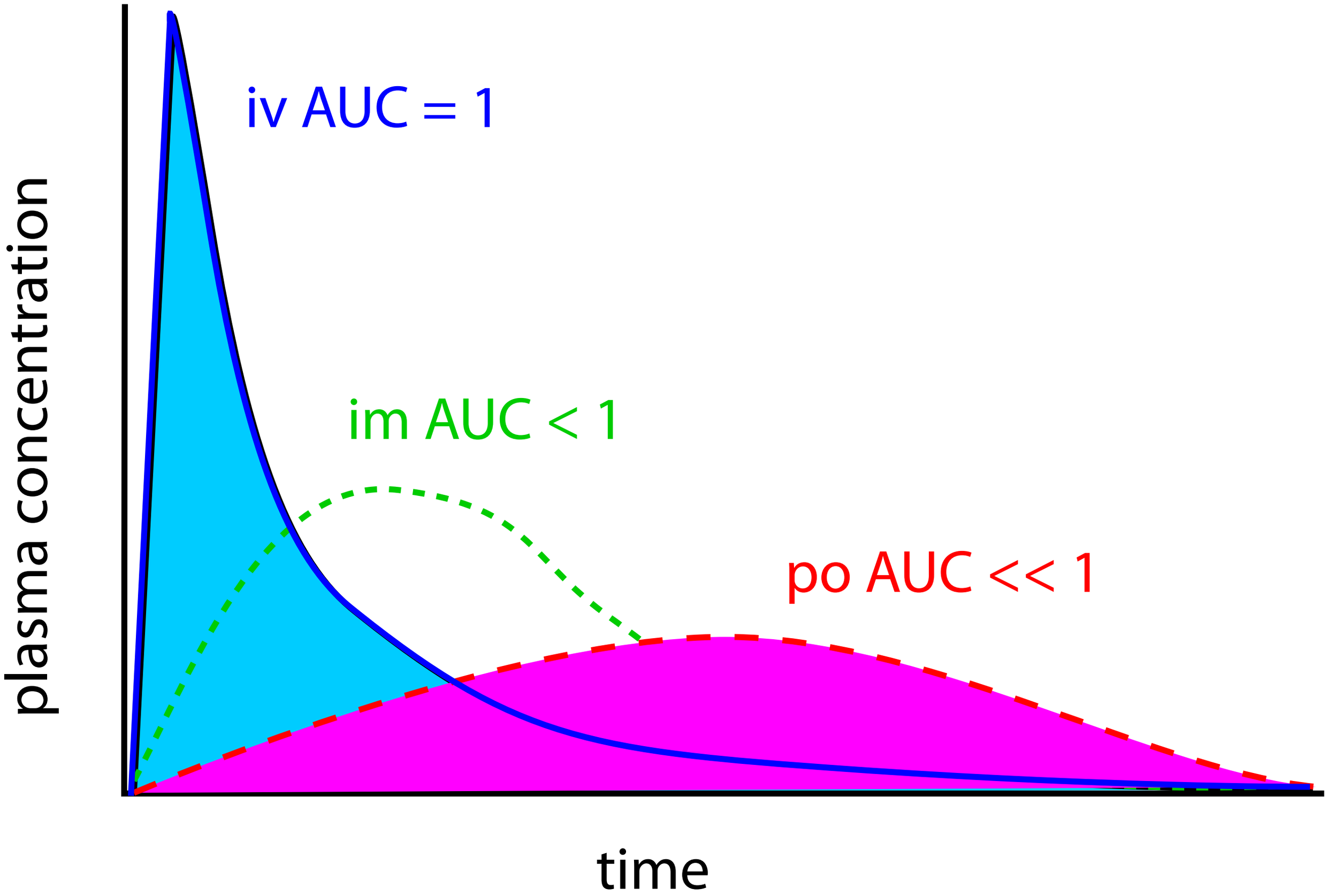
What would you do?

bioavailability

- the fraction of a drug that reaches the systemic circulation


iv
plasma concentration
time

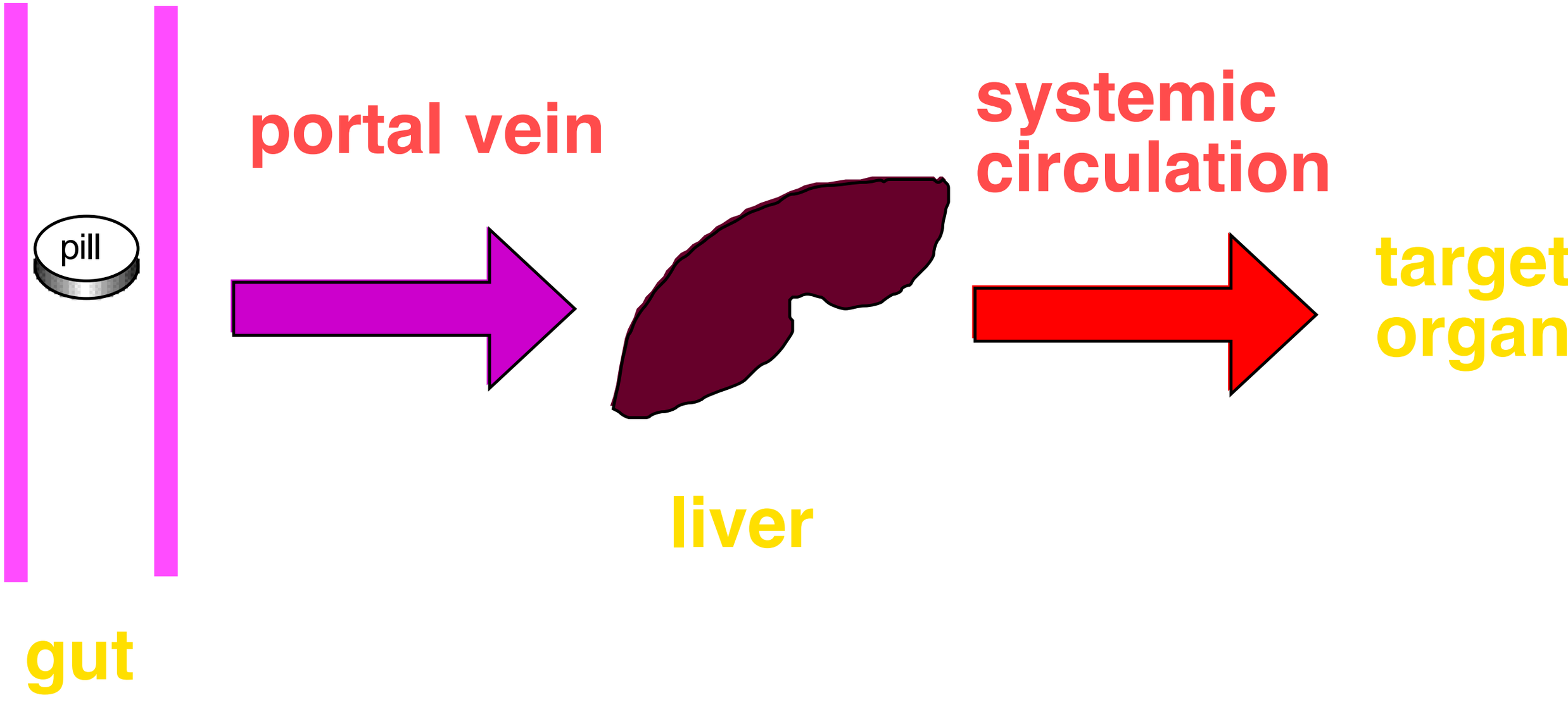

iv AUC = 1
plasma concentration
time


iv AUC = 1
im AUC < 1
po AUC << 1
plasma concentration
time

low bioavailability

- poor absorption
  - very hydrophilic drug
  - chemical instability
  - drug formulation
- first pass metabolism

first pass metabolism



bioequivalence

- same bioavailability
  - AUC
  - peak concentration (C_{max})
  - time to peak (T_{max})
- same effects

plasma concentration

C_{max}

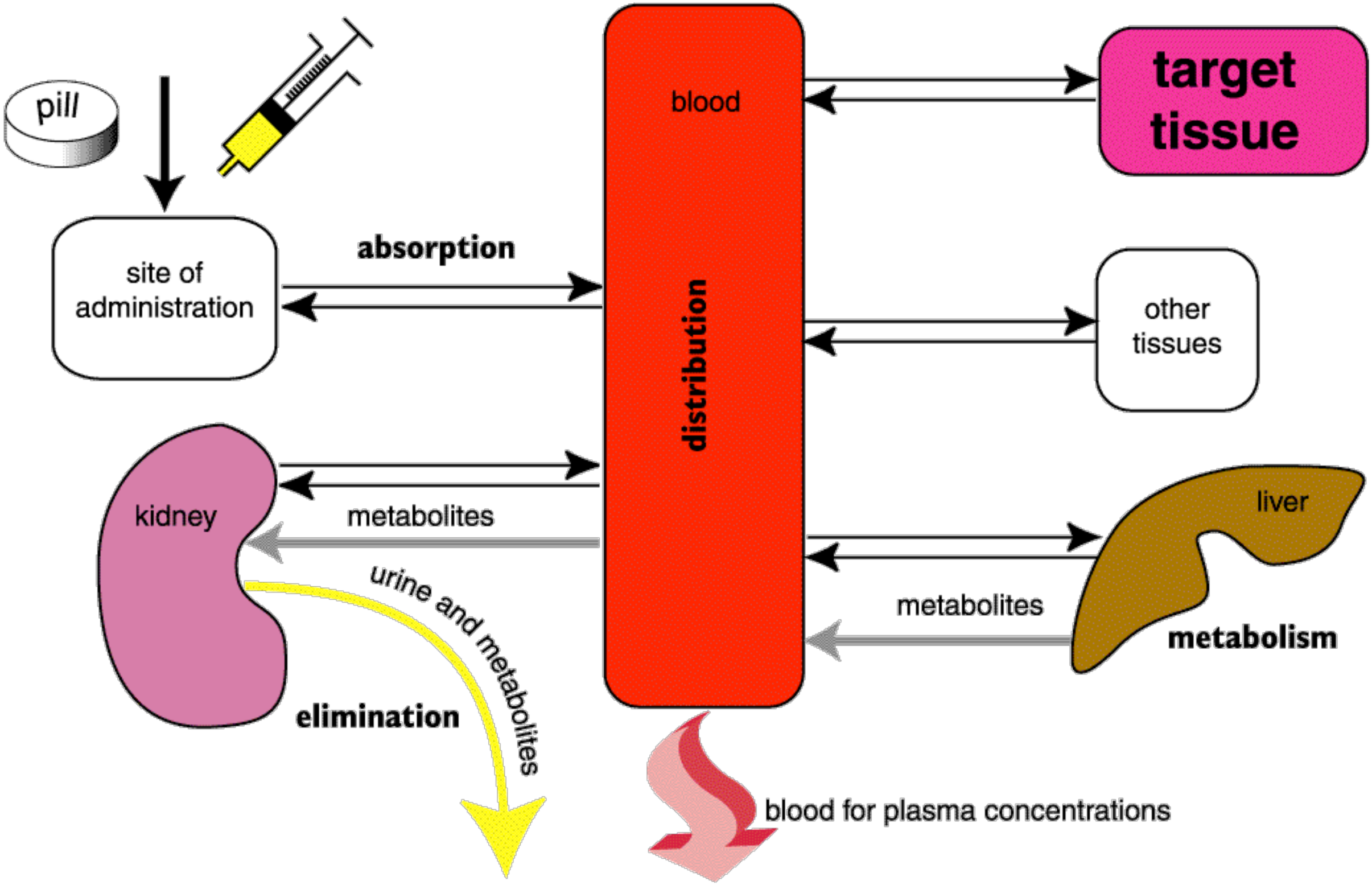
formulation 1

formulation 2

T_{max}

time

pharmacokinetics

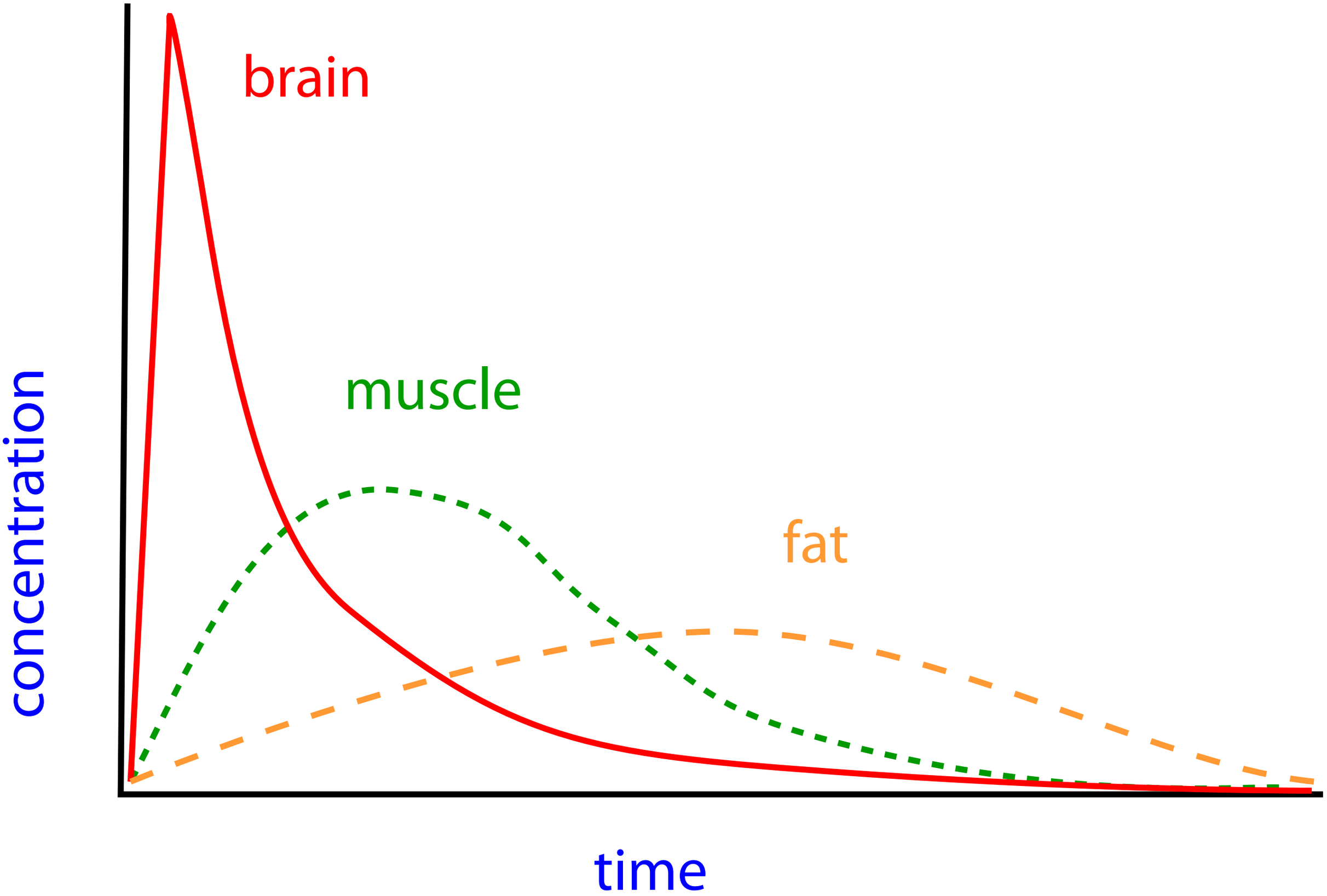


distribution

- the movement of drug from the circulation to the tissues and back

distribution

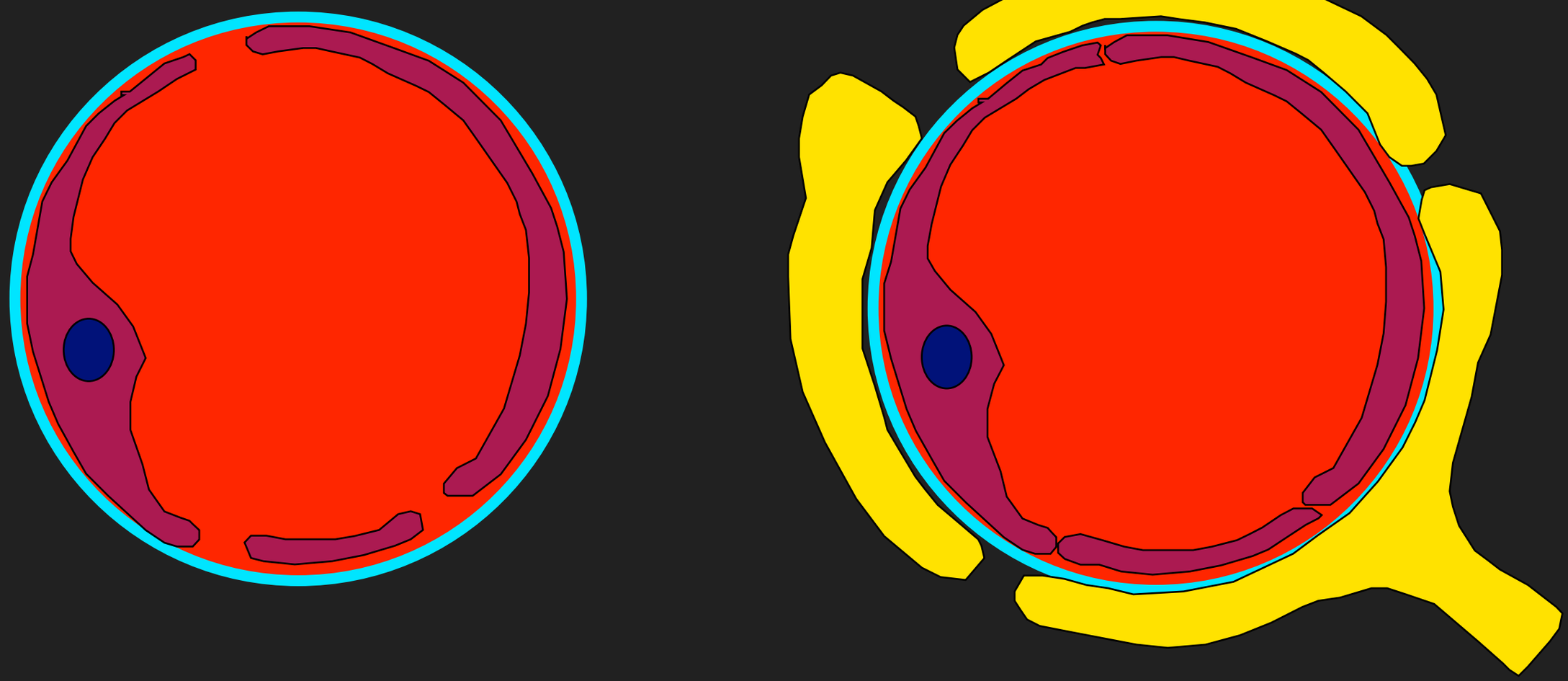
- blood flow
- capillary permeability
  - capillary structure
  - drug structure
  - carrier proteins (efflux pumps)
- protein binding


brain
muscle
fat
concentration
time

capillary structure

brain capillary

normal capillary



blood brain barrier

- no access for ionised drugs
  - aminoglycosides
  - penicillins
- lipid soluble drugs rapidly equilibrate and rapidly redistribute
  - anaesthetics
- P glycoprotein pumps many drugs out
  - also cancer cells
  - also bacteria

drug structure

- size
  - most drugs c 200Da
  - peptides c 5,000Da
  - proteins c 50,000 Da
- lipid solubility
  - oil / water partition coefficients

distribution

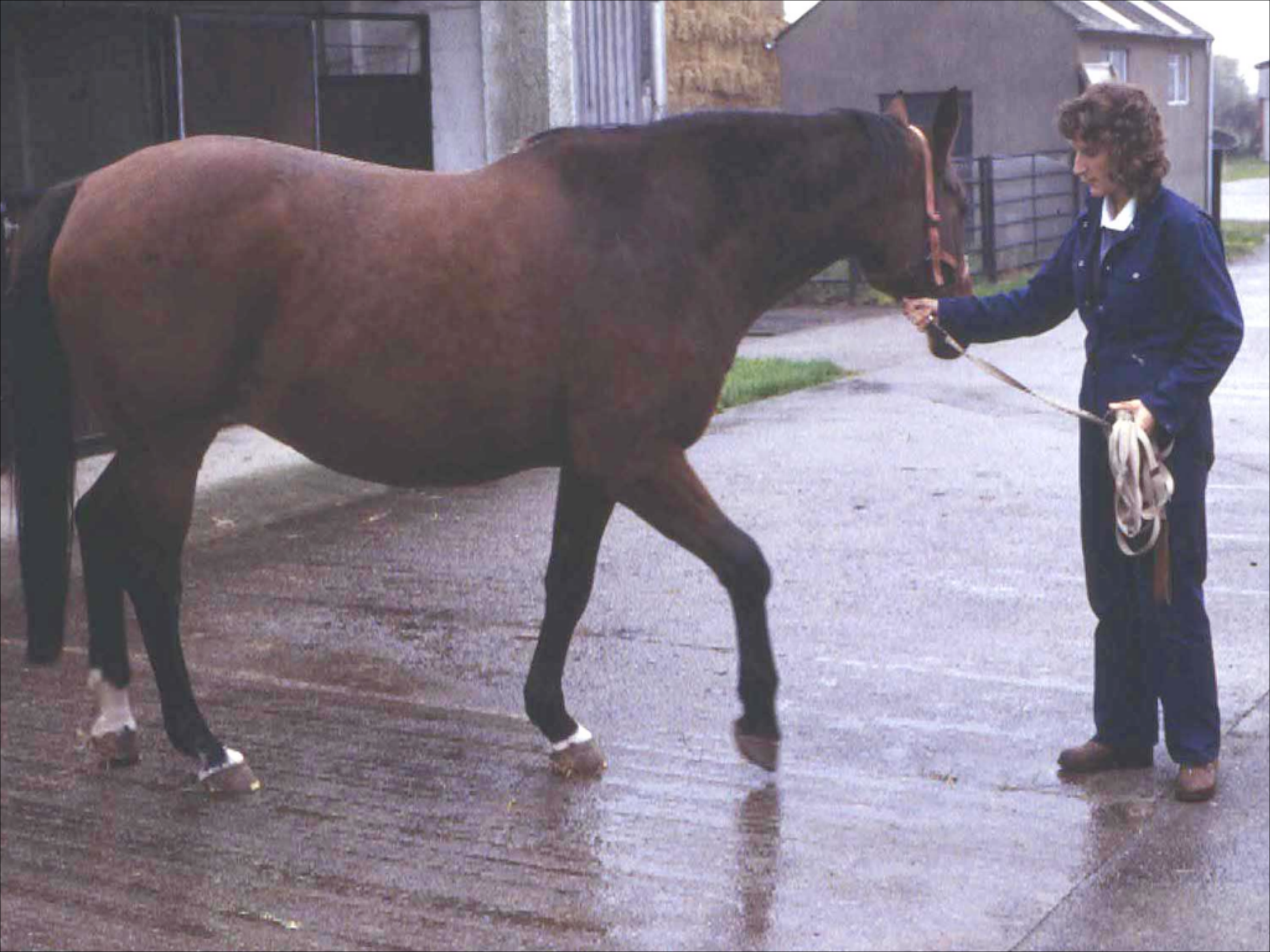
- blood flow
- capillary permeability
- protein binding

protein binding

- many drugs are bound to albumin
- keeps drugs in circulation
- free drug concentration low
  - only free drug is active

factors affecting protein binding

- other drugs
  - there are usually more binding sites than drug molecules, but if two highly bound drugs are given together, one drug may displace the other resulting in more free (active) drug than expected
  - sulphonamides often saturate binding sites
- hypoproteinaemia
  - liver disease
- (body temperature)
- (pH)



protein binding

- needs phenylbutazone
- may be on warfarin
- may also need surgery
  - thiopentone

drug distribution

drug distribution

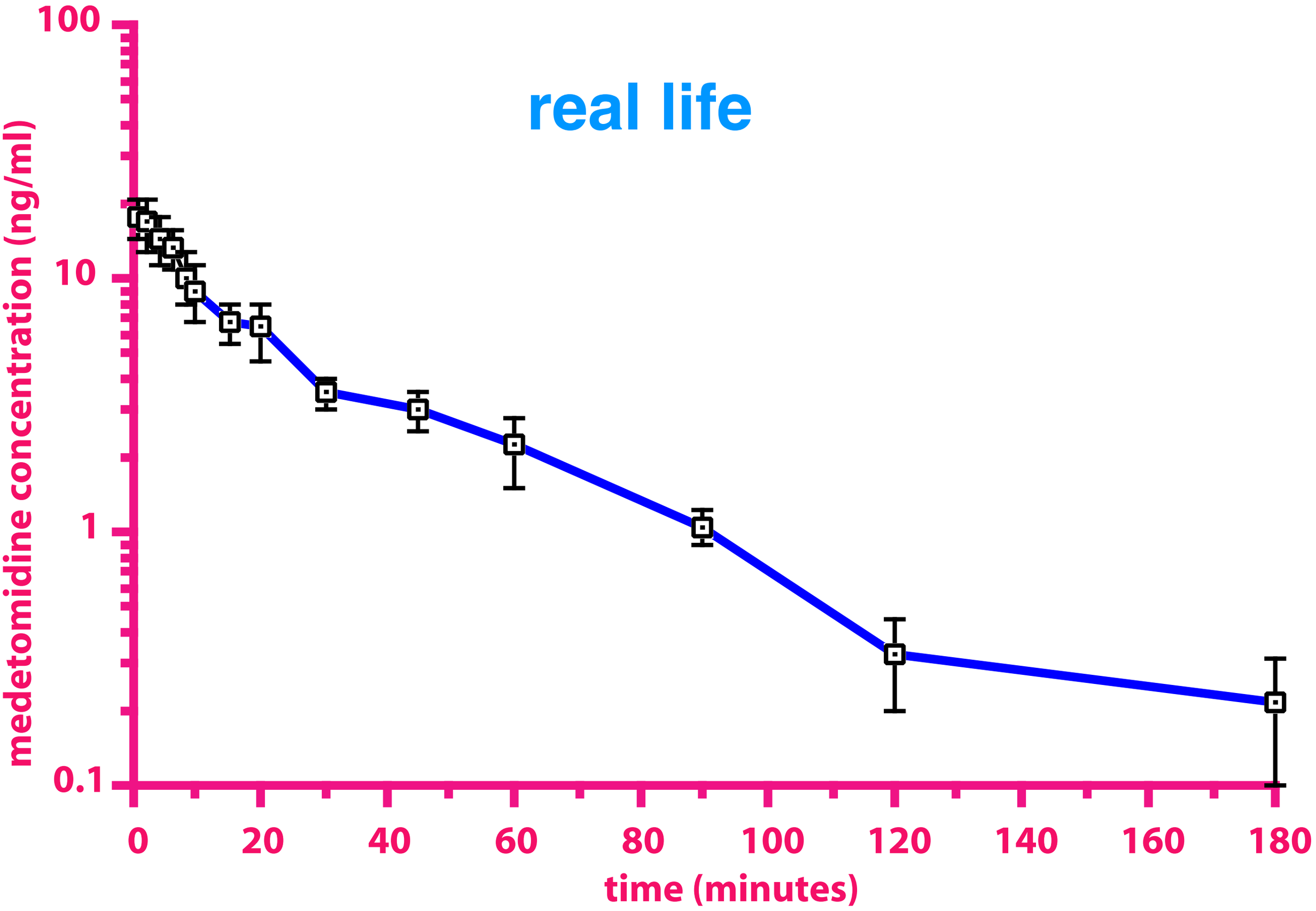
distribution phase

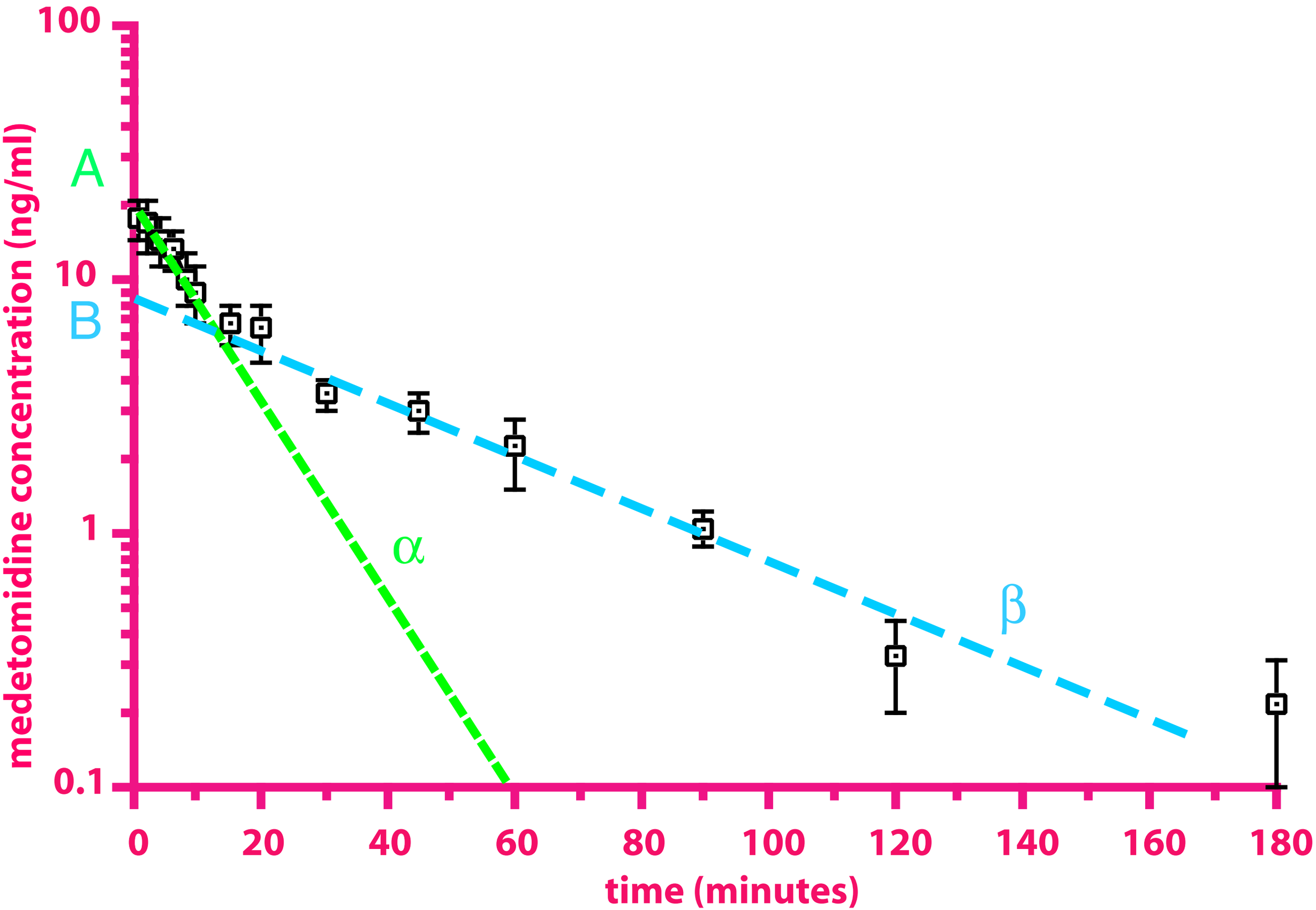
elimination phase

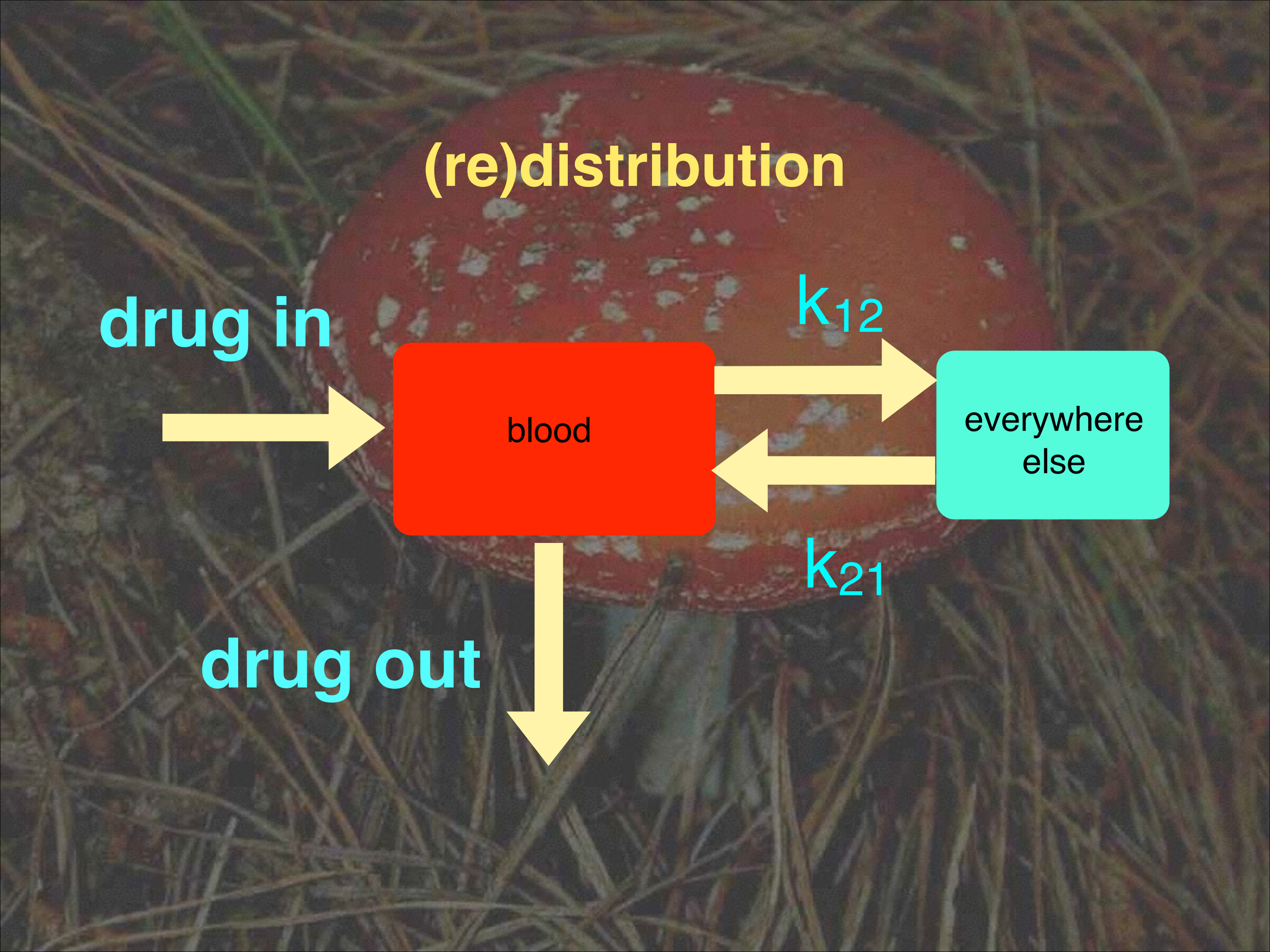
log plasma concentration

time

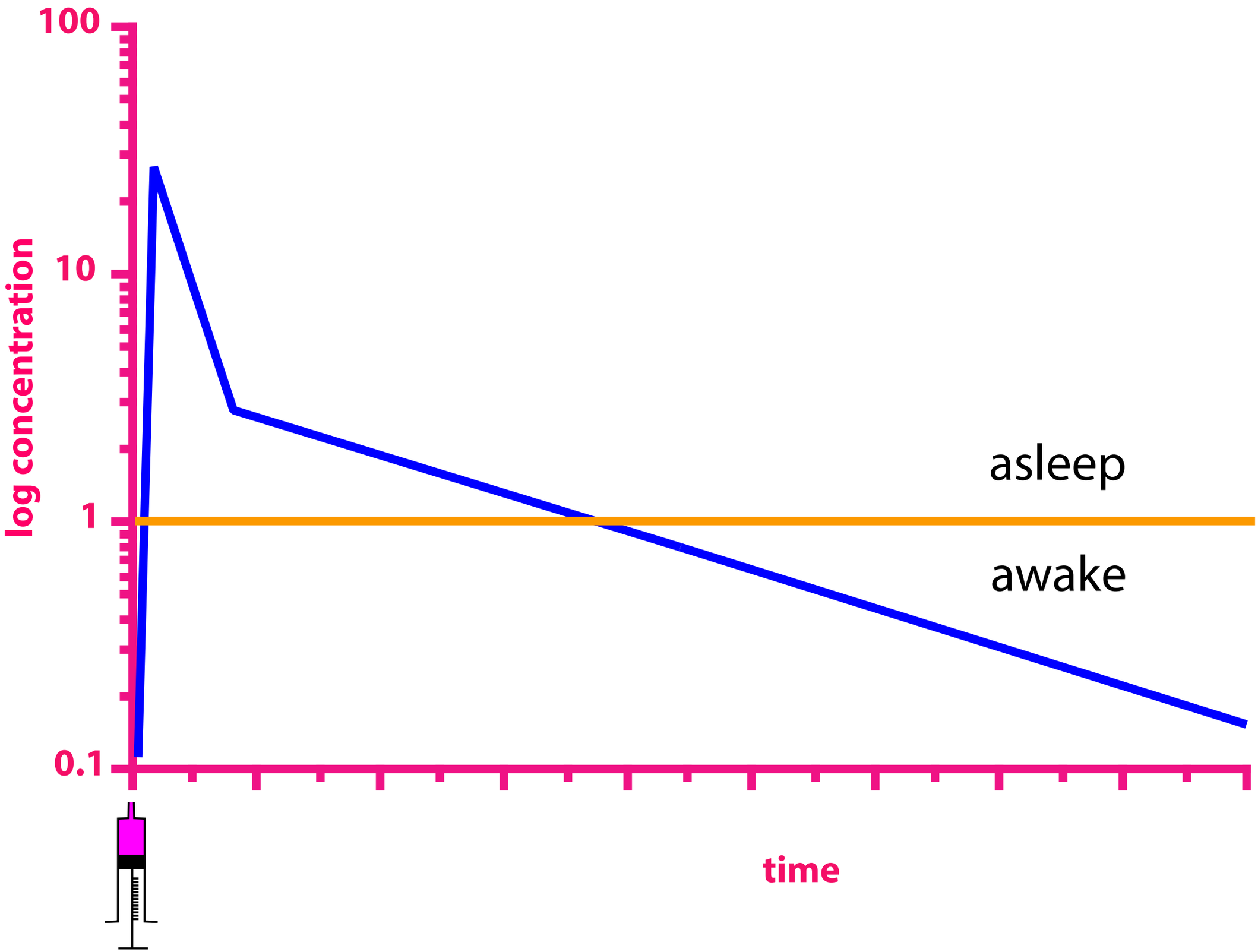
real life


100
10
1
0.1
medetomidine concentration (ng/ml)
0
20
40
60
80
100
120
140
160
180
time (minutes)

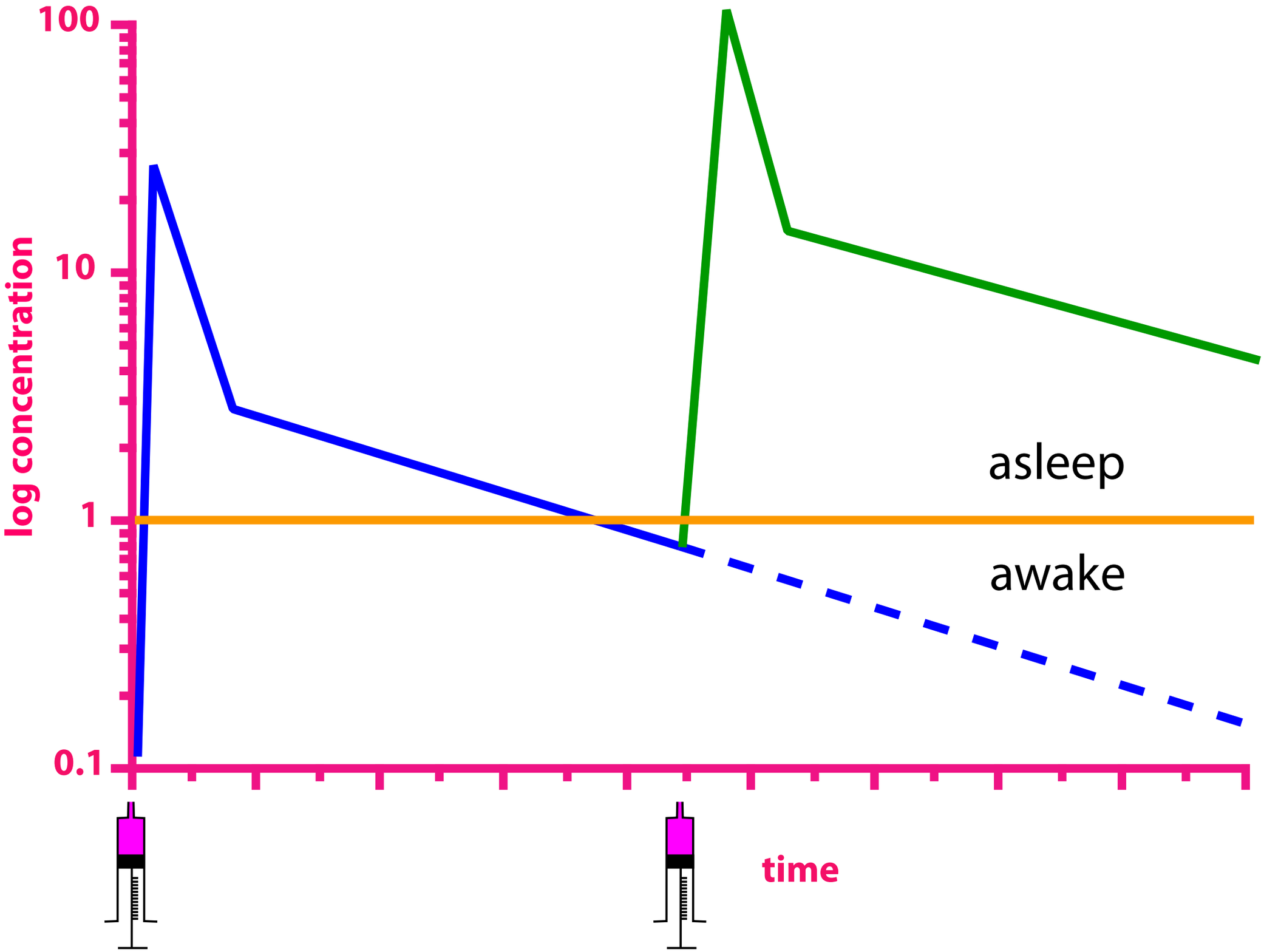

100
10
1
0.1
A
B
α
β
medetomidine concentration (ng/ml)
0
20
40
60
80
100
120
140
160
180
time (minutes)

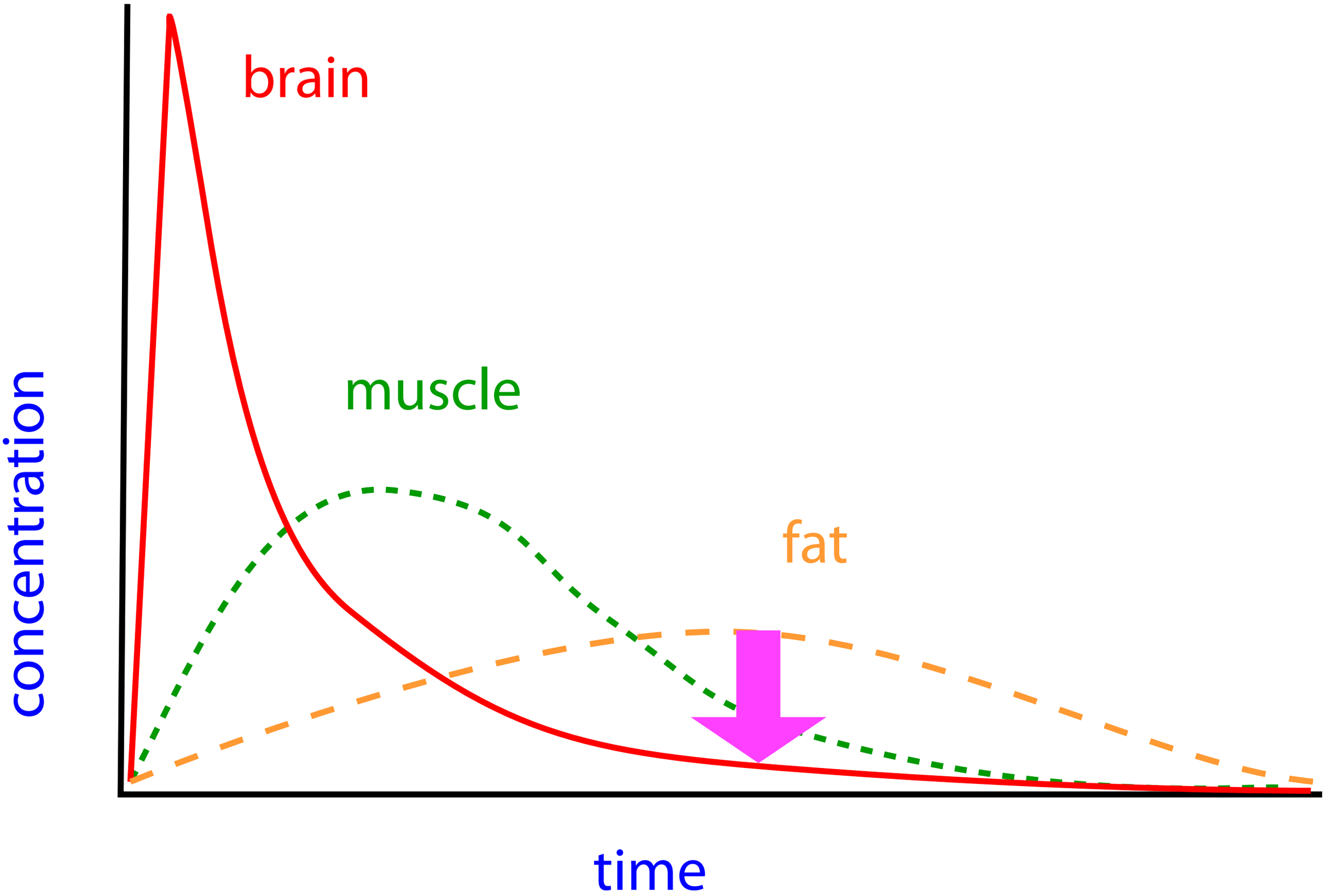

(re)distribution
drug in
k_{12}
blood
everywhere else
k_{21}
drug out

effective plasma levels

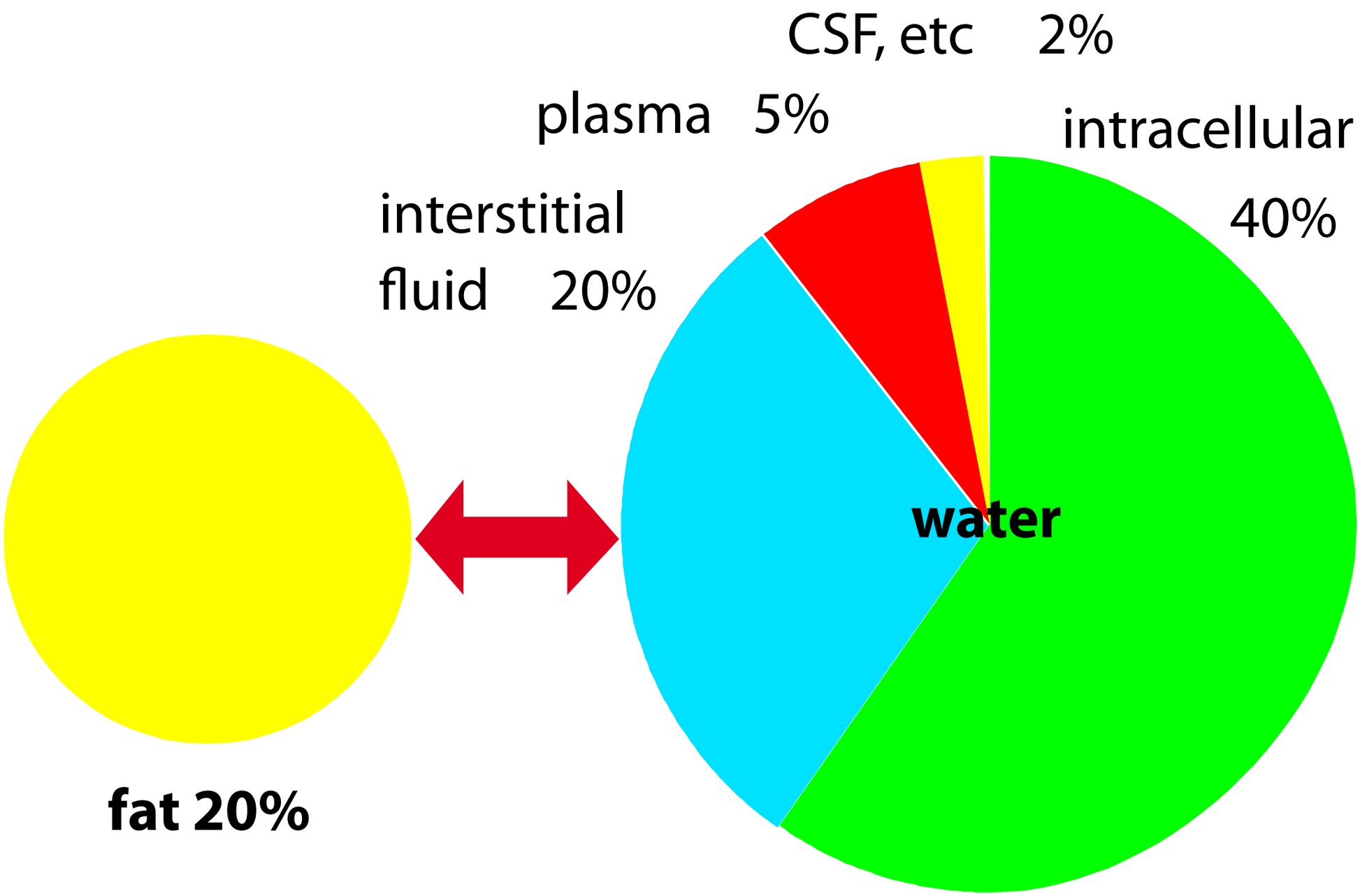


effective plasma levels




brain
muscle
fat
concentration
time

fluid compartments



volume of distribution

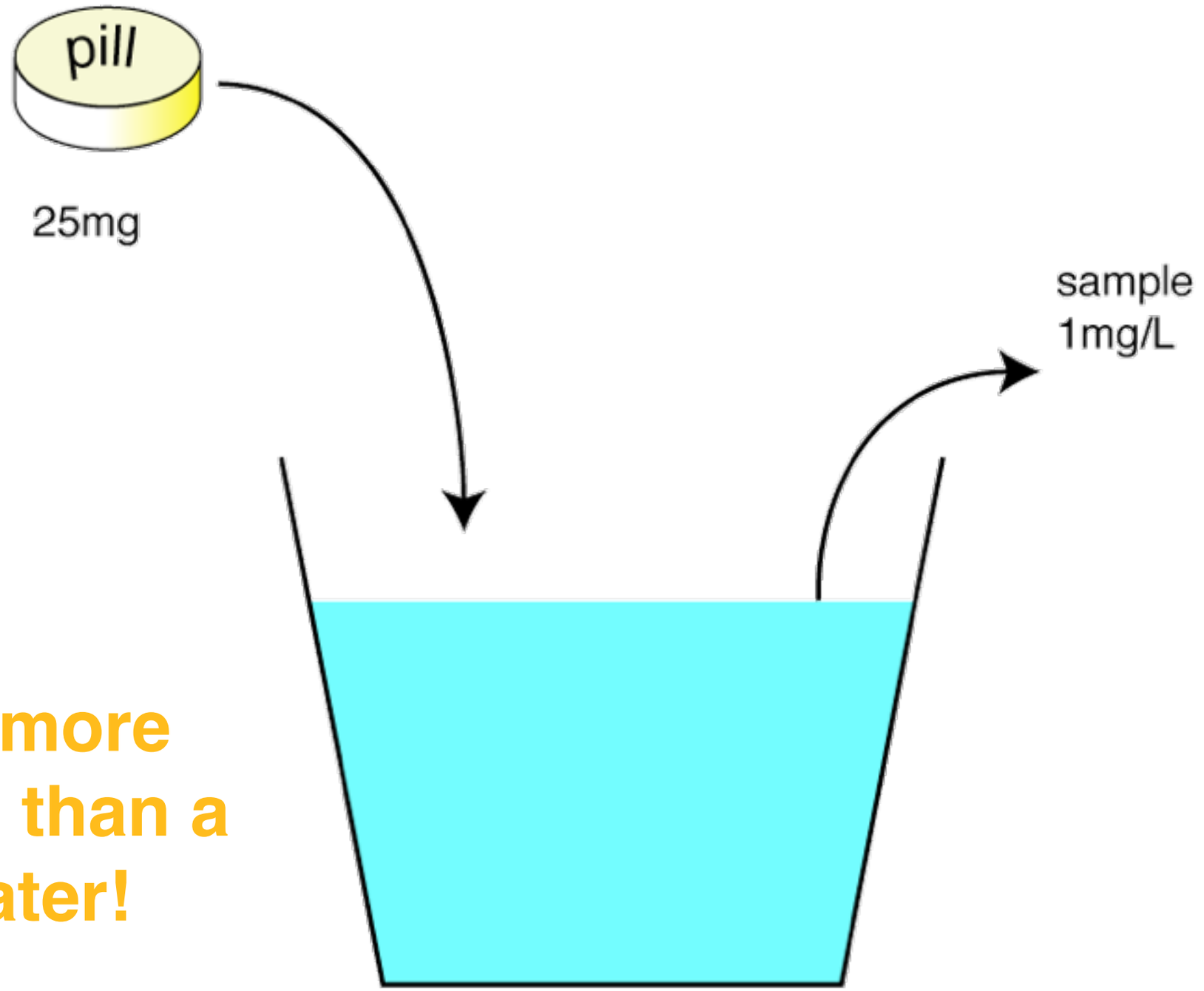
- Vd is the volume a drug would occupy if it was evenly distributed at the same concentration as in the plasma

Vd

$$V_d = \frac{Q}{C_p}$$

If 25mg of drug results in a plasma concentration of 1mg/L then $V_d = 25/1 = 25L$

Vd



- **animals are more complicated than a bucket of water!**

$$V_d$$

$$V_d C_p = Q$$

If Vd = 25L and plasma concentration = 1mg/L, then dose = 25mg

Vd

- Vd does not correspond to any anatomical or physiological compartment
- but - can provide some information on where drug goes

Vd

- heparin - 50 mL/kg ~ plasma volume
- gentamicin - 250 mL/kg ~ ECF volume
- diazepam - 650 mL/kg ~ total body water
- morphine 5 L/kg ~ ?

Vd

- a large Vd implies that the drug is preferentially distributed somewhere - usually to fat - and is unavailable

Vd

- used to calculate doses to achieve target plasma levels
- but
  - individual variation
  - pathology

listeriosis

- meningitis
- sensitive to penicillin
- penicillin is not lipid soluble
- what do you do?

listeriosis

- meningitis breaks down BBB
- penicillin gets in
- penicillin kills Listeria
- meningitis clears up
- penicillin no longer gets in

treatment

- high dose benzylpenicillin sodium iv
- saline iv
- anti-inflammatory drugs?

distribution

- drugs are usually distributed out of the blood to their site of action
- many drugs bind to plasma proteins and are unavailable for action or metabolism
- drugs are not distributed evenly throughout the body - each has a volume of distribution