Implementing receptor theory in PK-PD modeling

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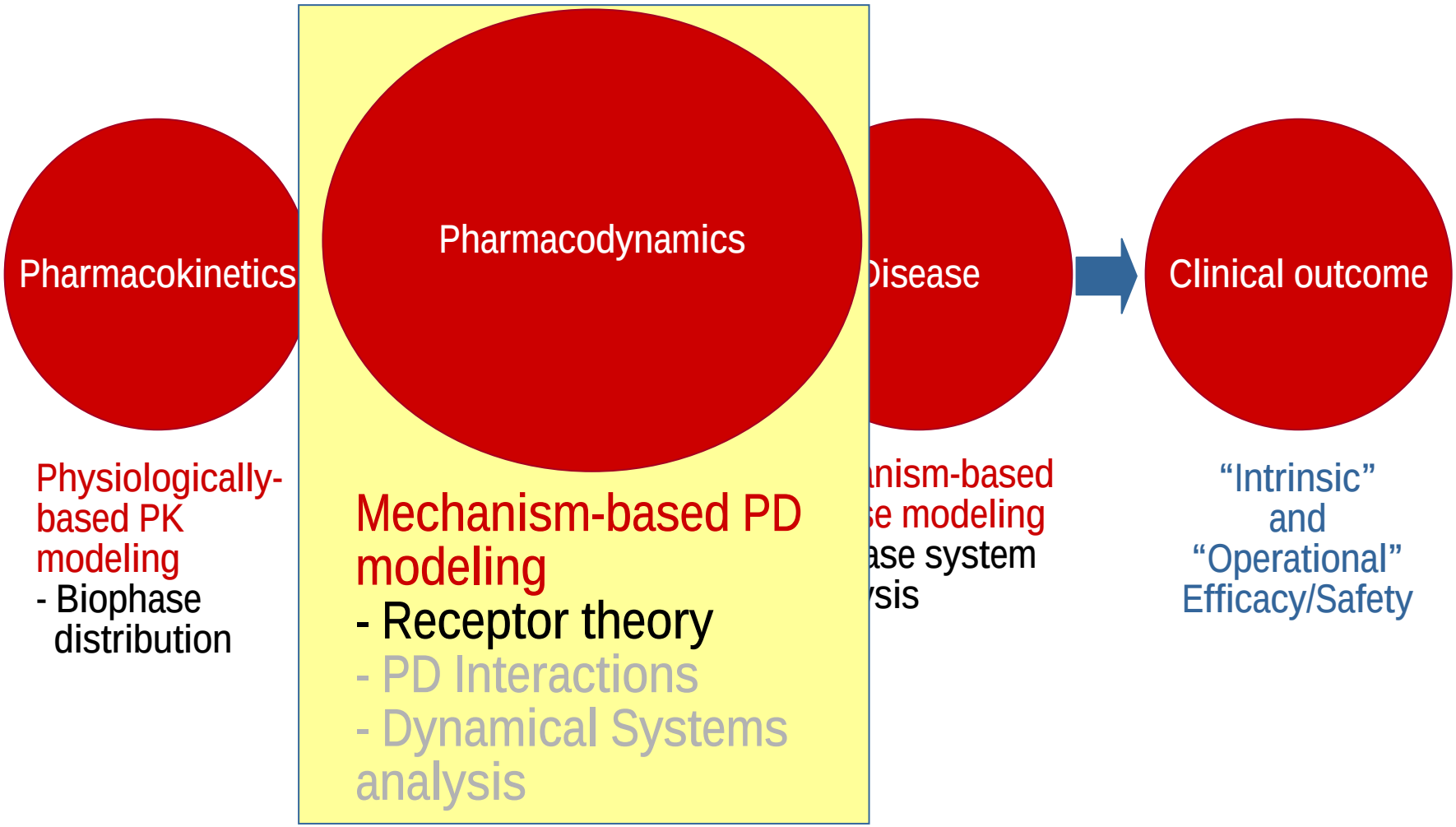
Mechanism-based PK-PD modeling
current status and future directions



Danhof M. et al., (2007) Ann. Rev. Pharmacol. Toxicol. 47: 357-400.

Mechanism-based PK-PD modeling
a pharmacologist's view

Describe processes on the causal chain between (plasma) concentration and effect

1. Target site distribution
2. Target binding and activation
3. Transduction processes
4. Pharmacodynamic interactions
5. Homeostatic feedback

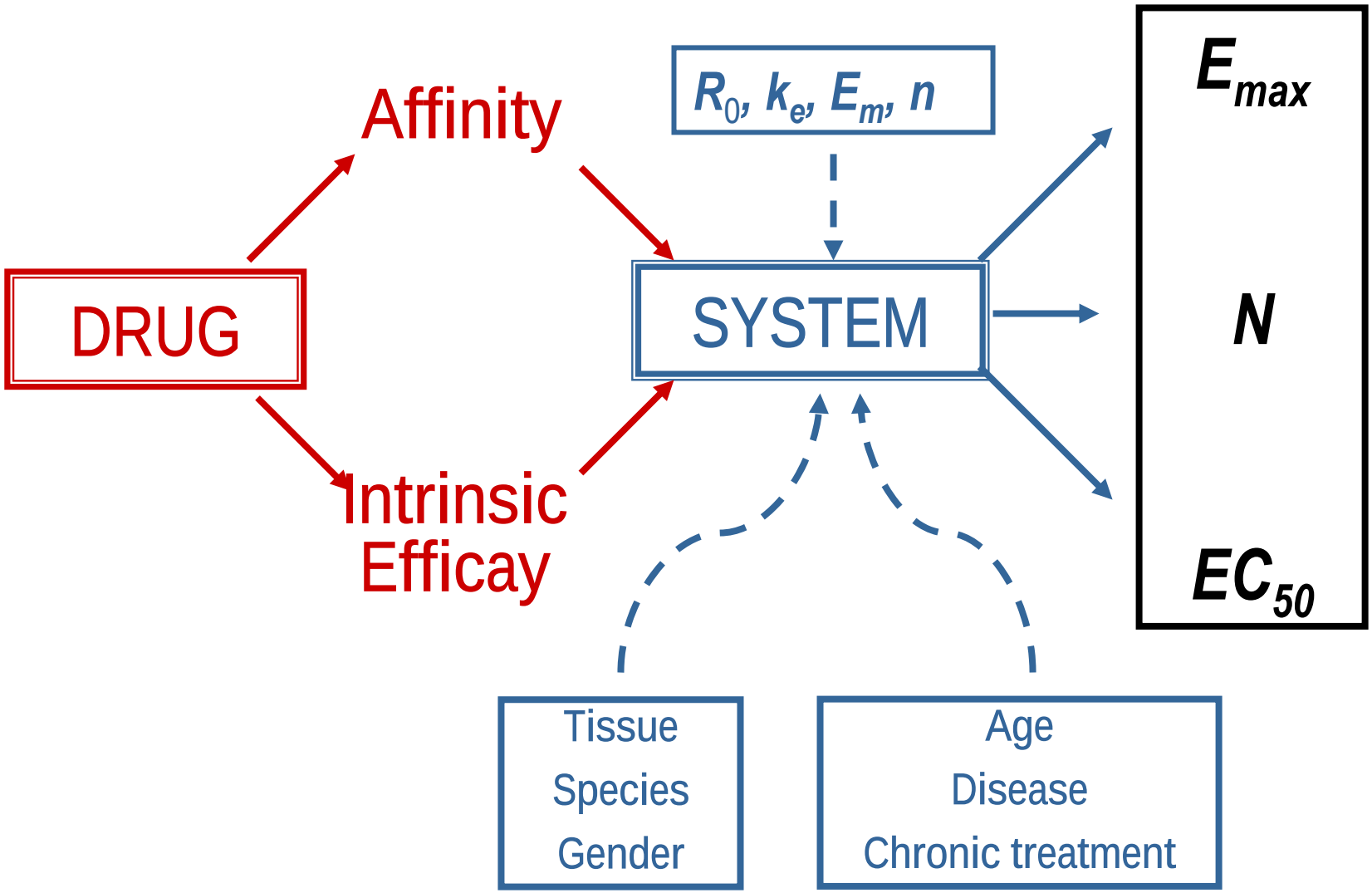
} "In Vivo" Transduction

Danhof M. et al., (2007) Ann. Rev. Pharmacol. Toxicol. 47: 357-400.

Implementing receptor theory in PK-PD modeling

Concentration-effect relationship

Concentration-effect relationships can differ between tissues, species and individuals



Receptor theory for prediction of concentration-effect relationships

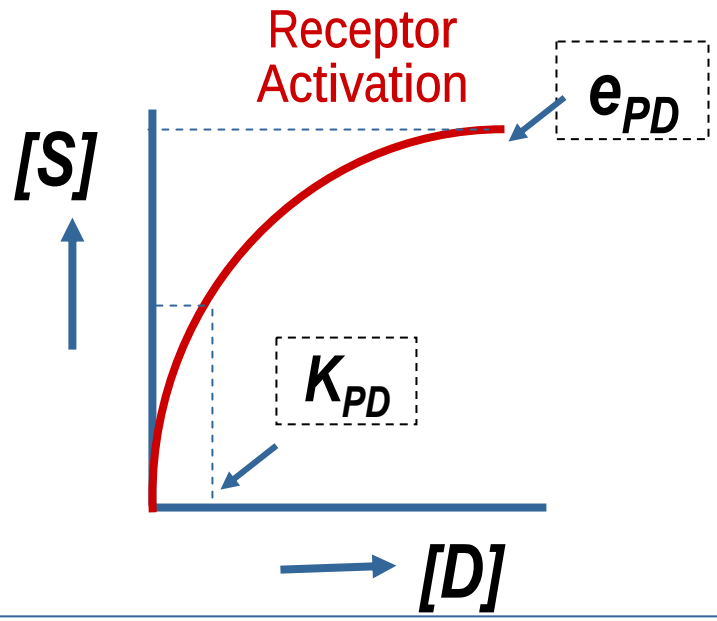
- *In vivo* concentration-effect relationships
- Tissue selectivity of drug effects
- Interspecies differences in concentration-effect relationships
- Tolerance and sensitization
- Intra- and inter-individual variability

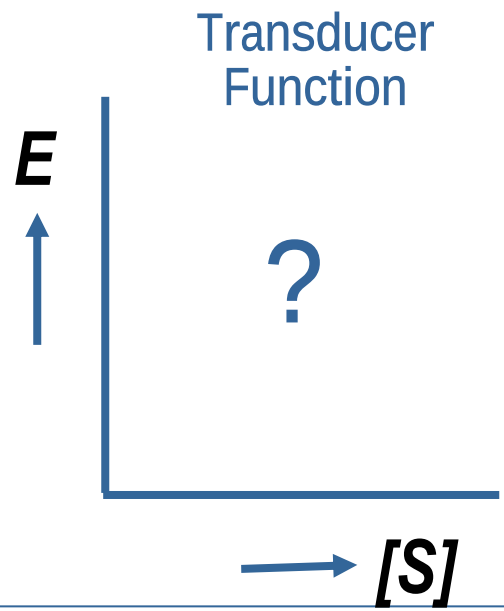
Receptor function as a determinant of drug effect

Receptor theory for prediction of concentration-effect relationships

$$S = \frac{\varepsilon \times R_{tot} \times [D]}{K_{PD} + [D]} = \frac{e_{PD} \times [D]}{K_{PD} + [D]}$$

$$E = f([S])$$

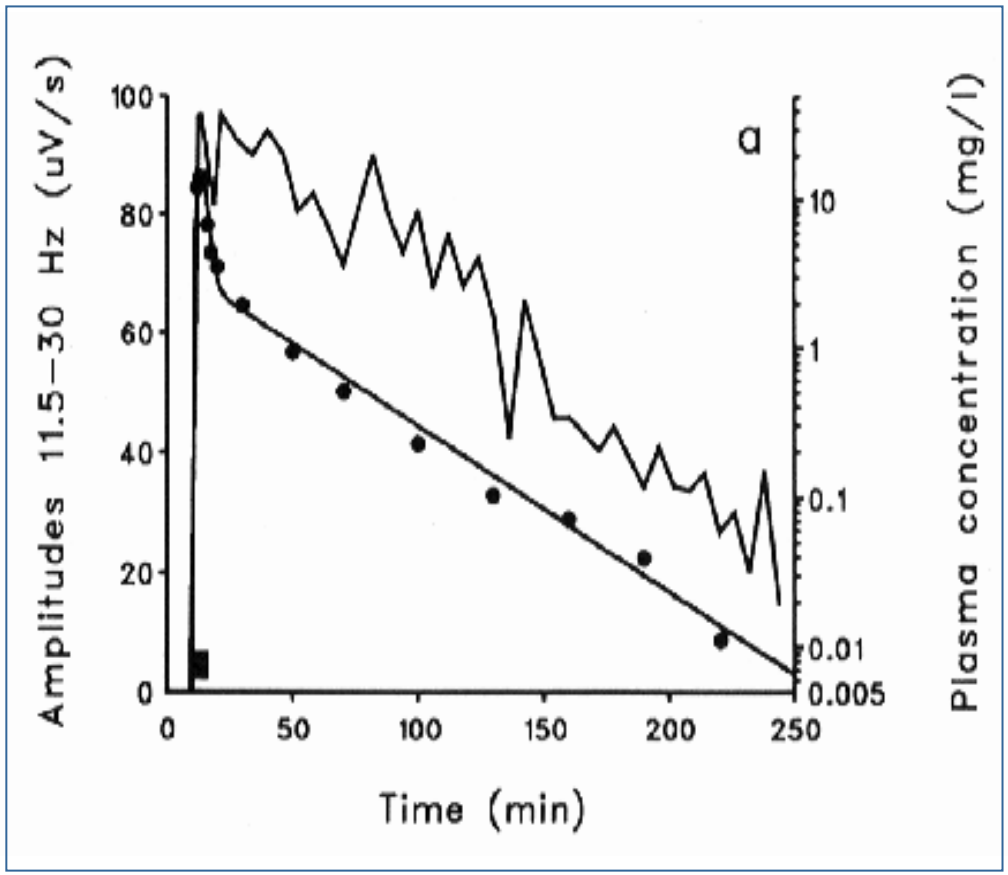




Identification of the receptor model application to $GABA_A$ receptor agonists

- Simultaneous analysis of the concentration-effect curves of flunitrazepam, midazolam, oxazepam and clobazam
- Assumption of a single and 'unique' transducer function (non-parametric; continuously increasing function)
- Description of the receptor activation process on basis of a hyperbolic function
- 'Comparative' method for estimation of the drug-specific parameters

Midazolam: plasma concentrations and EEG effect in individual rats

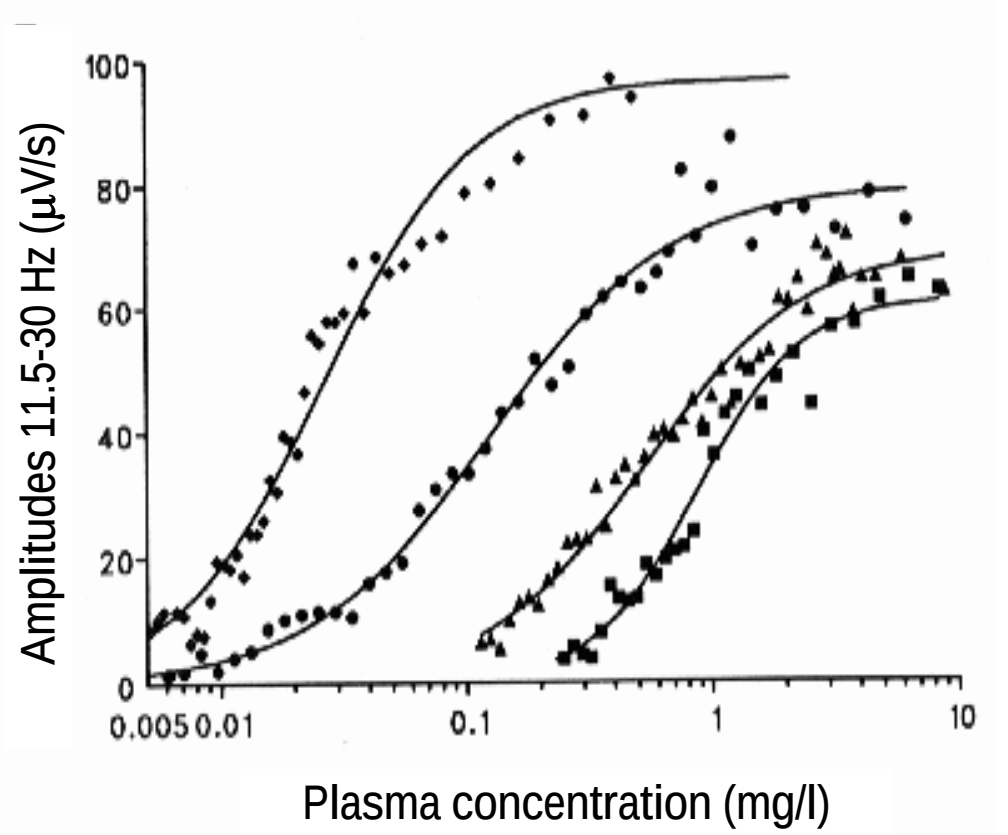


PK-PD

- Simultaneous monitoring of plasma concentration and EEG effect results in data sets that can be subjected to PK-PD modelling
- In this manner concentration effect relationships are obtained in individual rats

From: Mandema ***et al***., Br. J. Pharmacol. 102: 663-668 (1991)

EEG effect: benzodiazepines differ in potency and intrinsic activity



PK-PD

- ***In vivo*** concentration-EEG effect relationships of 4 benzodiazepines:

  Flunitrazepam (◆)
  Midazolam (●)
  Oxazepam (▲) and
  Clobazam (■)

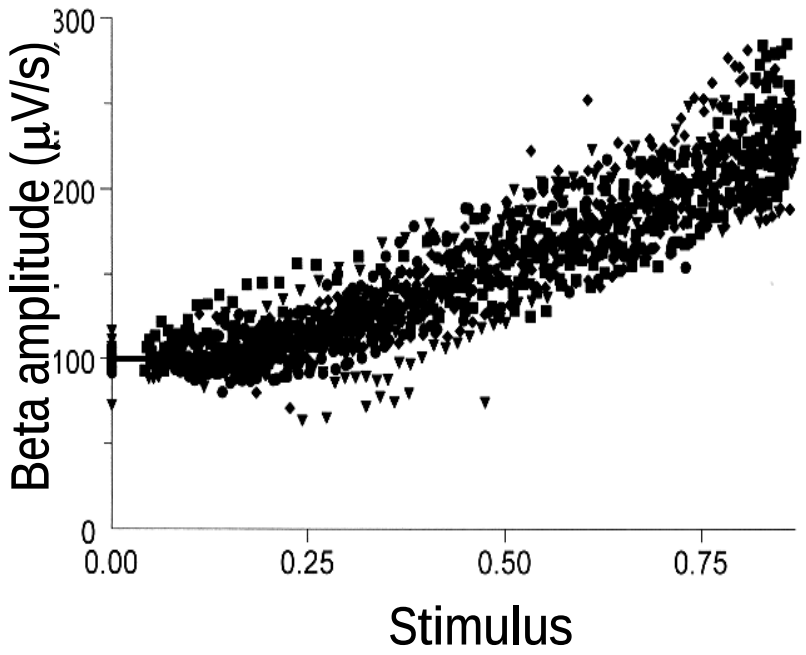
From: Mandema ***et al.***, J. Pharmacol. Exp. Ther. 257: 472-478 (1991)

Non-linear transducer function with no saturation at high stimulus intensities

Drug-specific receptor interaction parameters

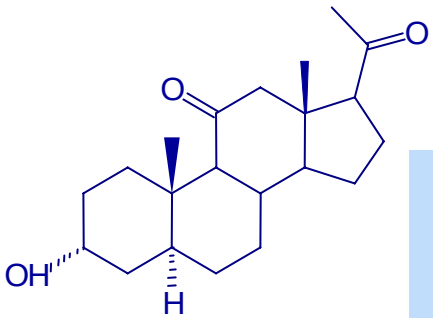
Drug	K_{PD} ng.ml^{-1}	e_{PD}
Flunitrazepam	21 ± 2.1	1
Midazolam	43 ± 6.0	0.87 ± 0.03
Oxazepam	411 ± 49	0.90 ± 0.04
Clobazam	782 ± 86	0.79 ± 0.03

System-specific transducer function

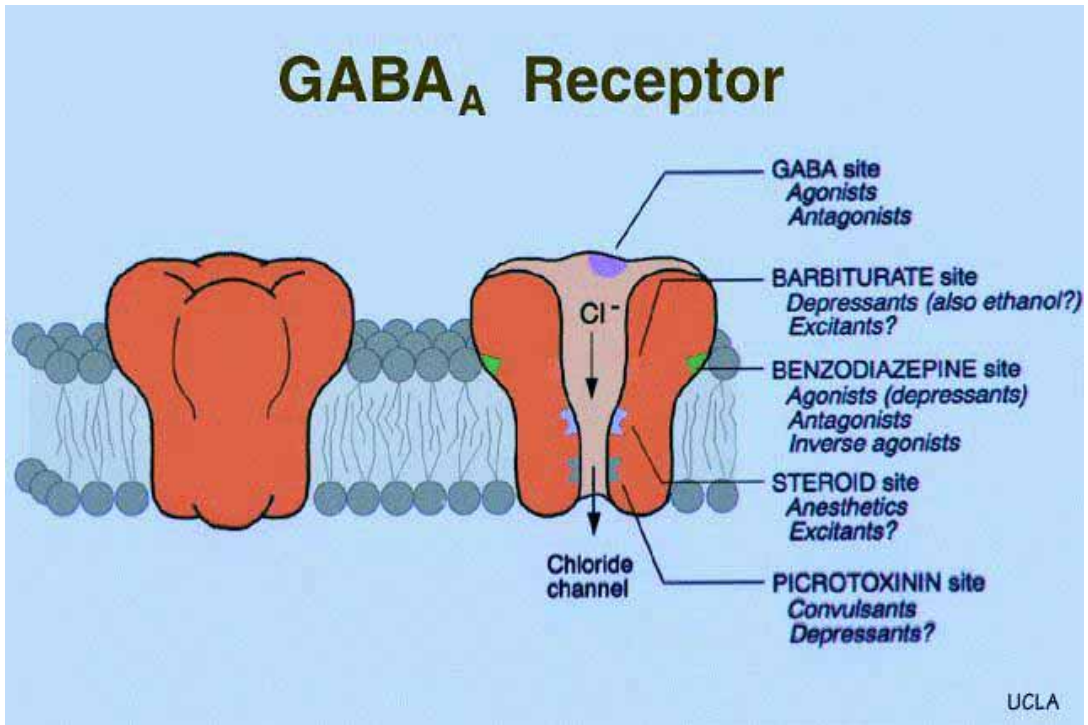


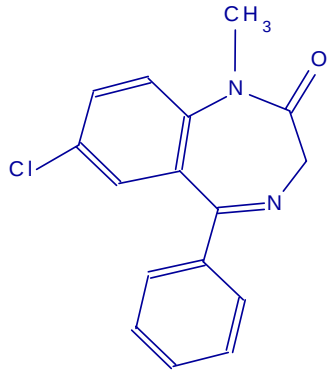
From: Tuk ***et al.***, J. Pharmacol. Exp. Ther. 289: 1067-1074 (1999)

Neurosteroids and benzodiazepines share the same transducer function



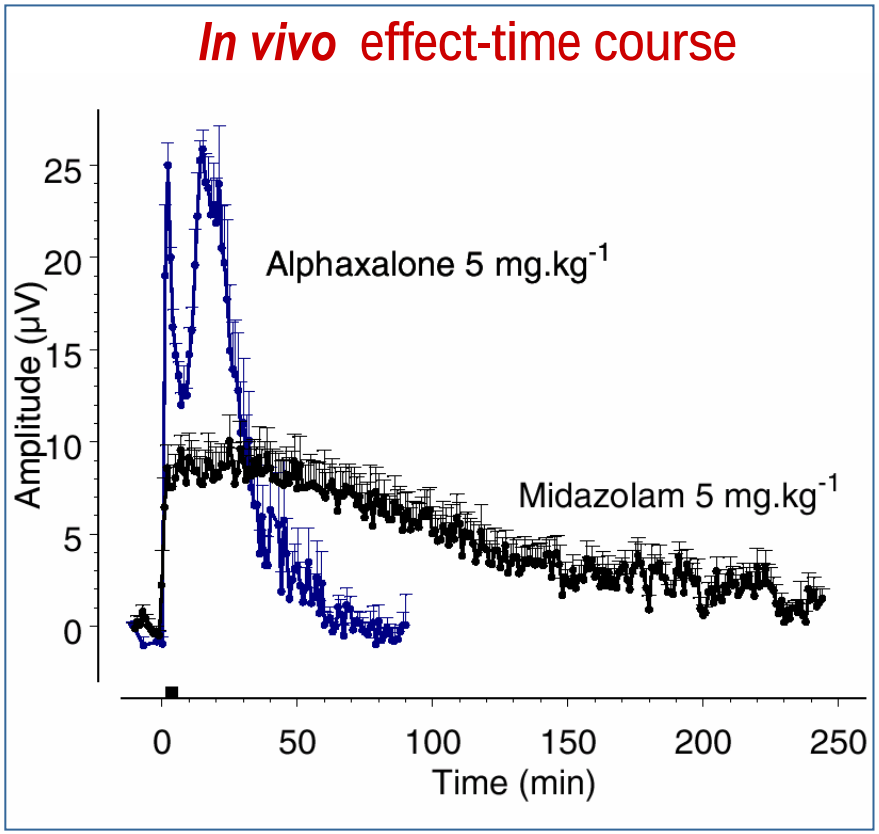
Alphaxalone
Pregnanolone
ORG 21465
ORG 20599

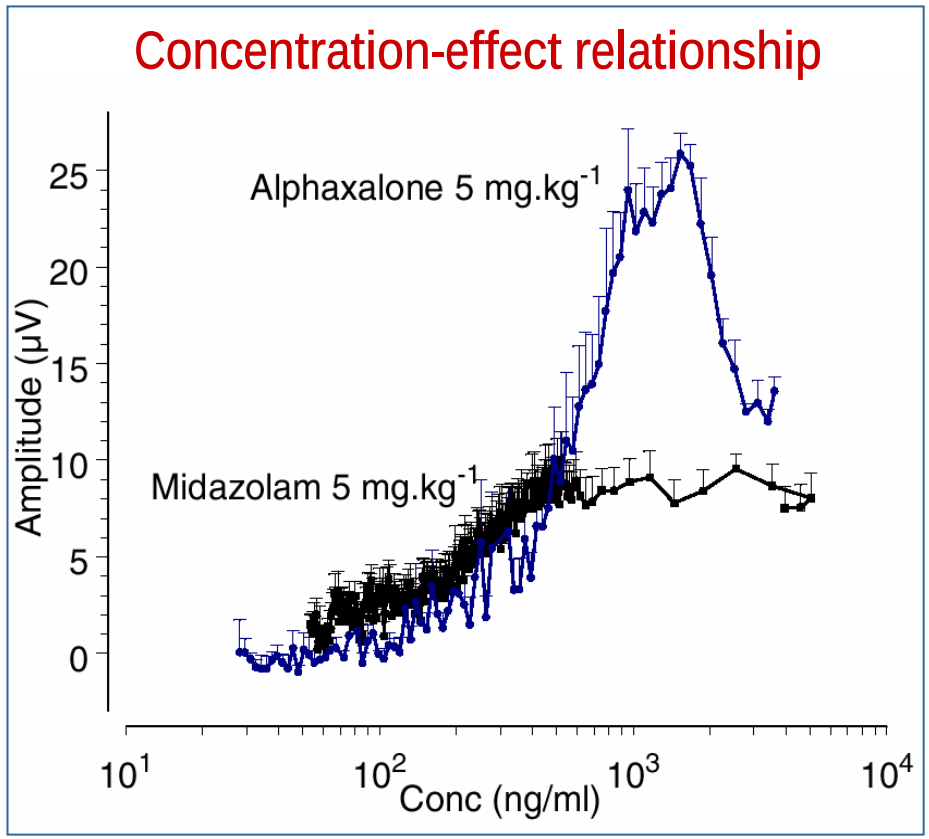




Diazepam
Flunitrazepam
Midazolam
Clobazam
Zolpidem
Oxazepam
Zopiclone
Bretazenil

EEG effects of alphaxalone and midazolam are quantitatively and qualitatively different

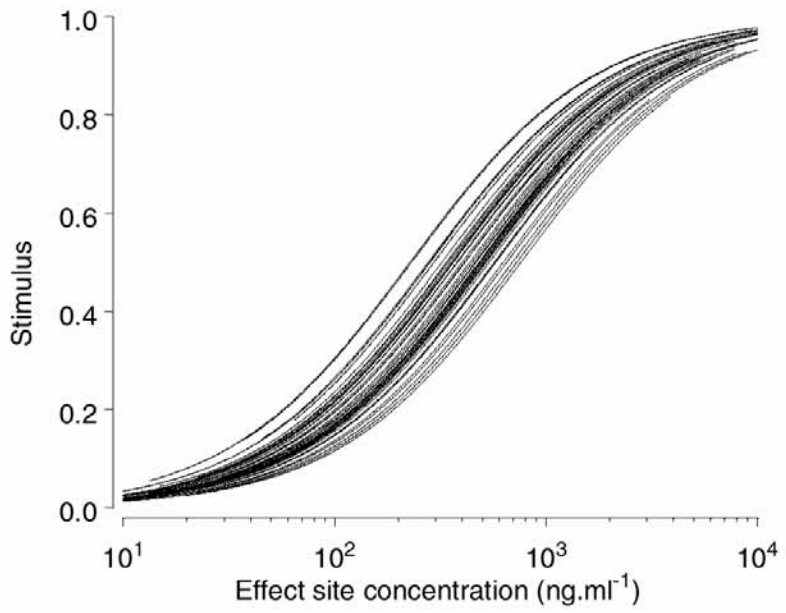




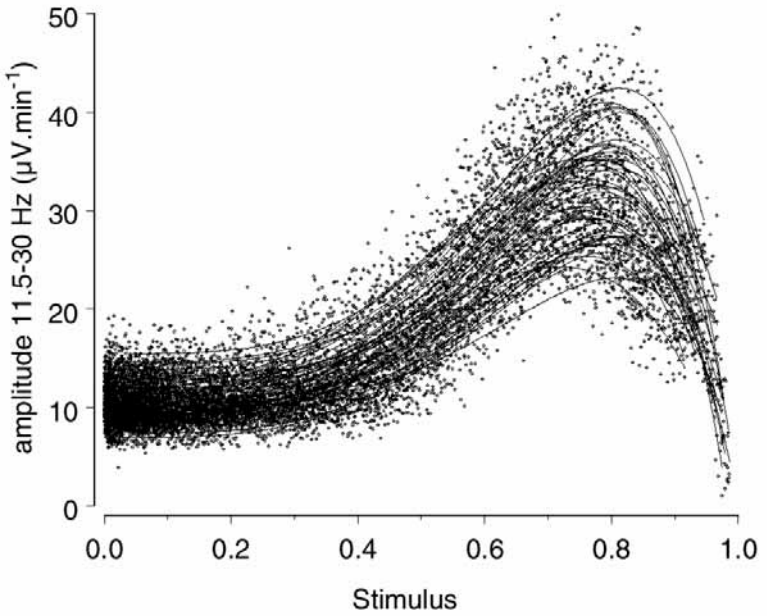
From: Visser ***et al***., J. Pharmacol. Exp. Ther. 302: 1158-1167 (2002)

A *parabolic function* describes the *stimulus-response* relationship of alphaxalone

Drug-receptor interaction



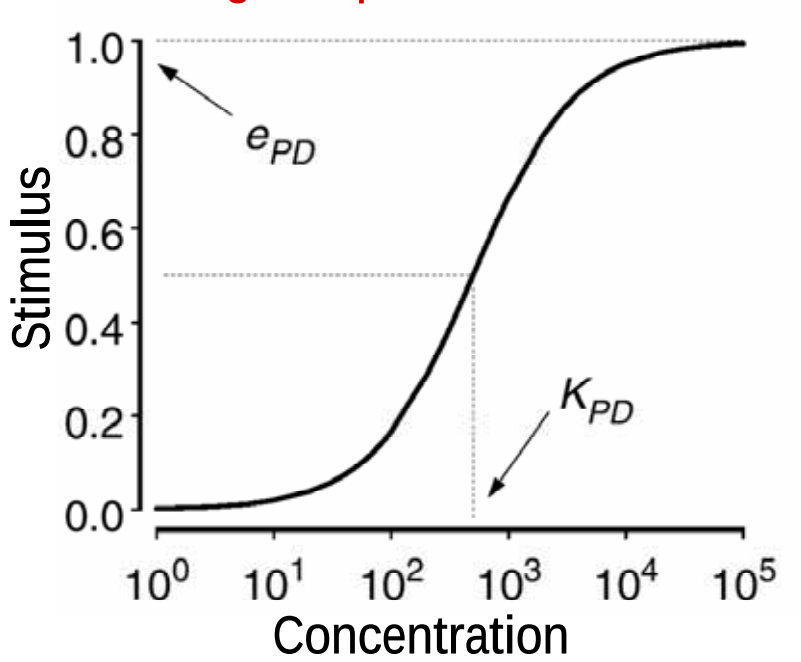
Stimulus-response relationship



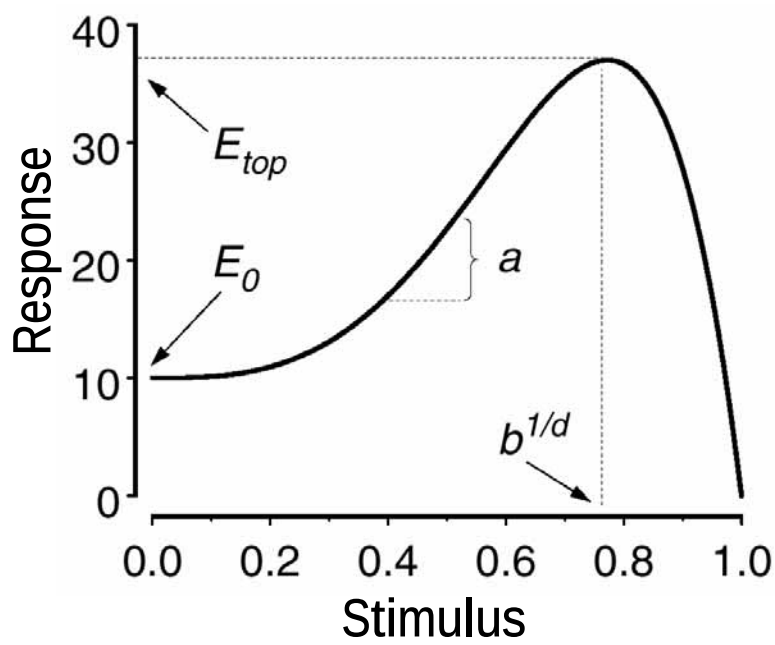
From: Visser ***et al***., J. Pharmacol. Exp. Ther. 302: 1158-1167 (2002)

Mechanism-Based PK-PD Model for Neurosteroids and Benzodiazepines

Drug-receptor interaction



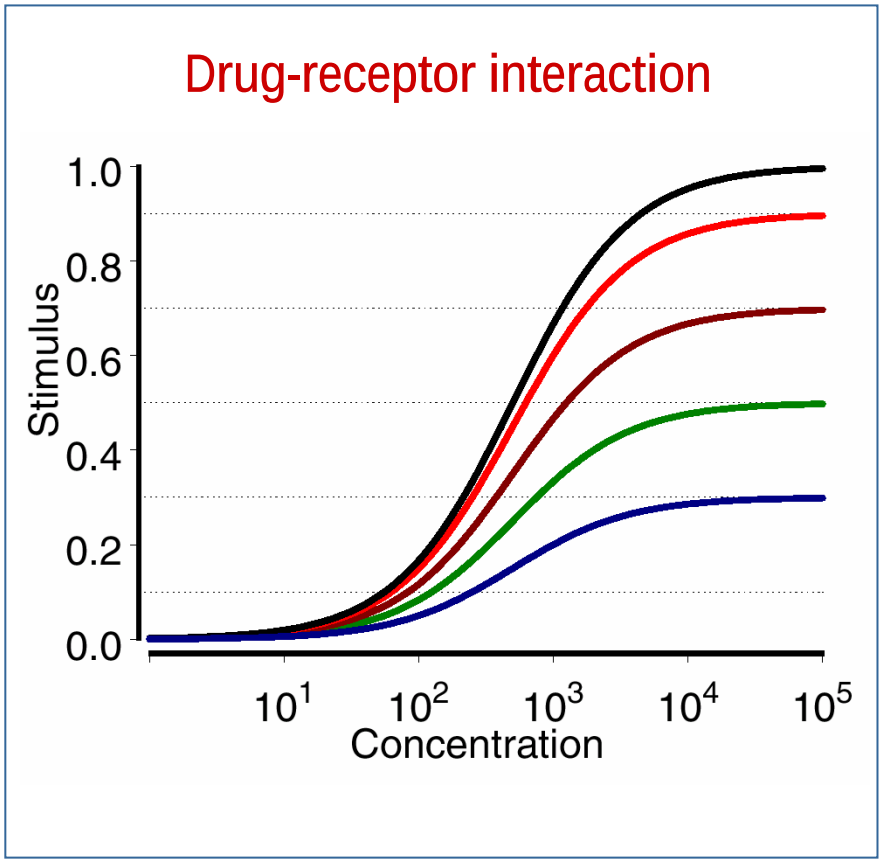
Stimulus-response relationship

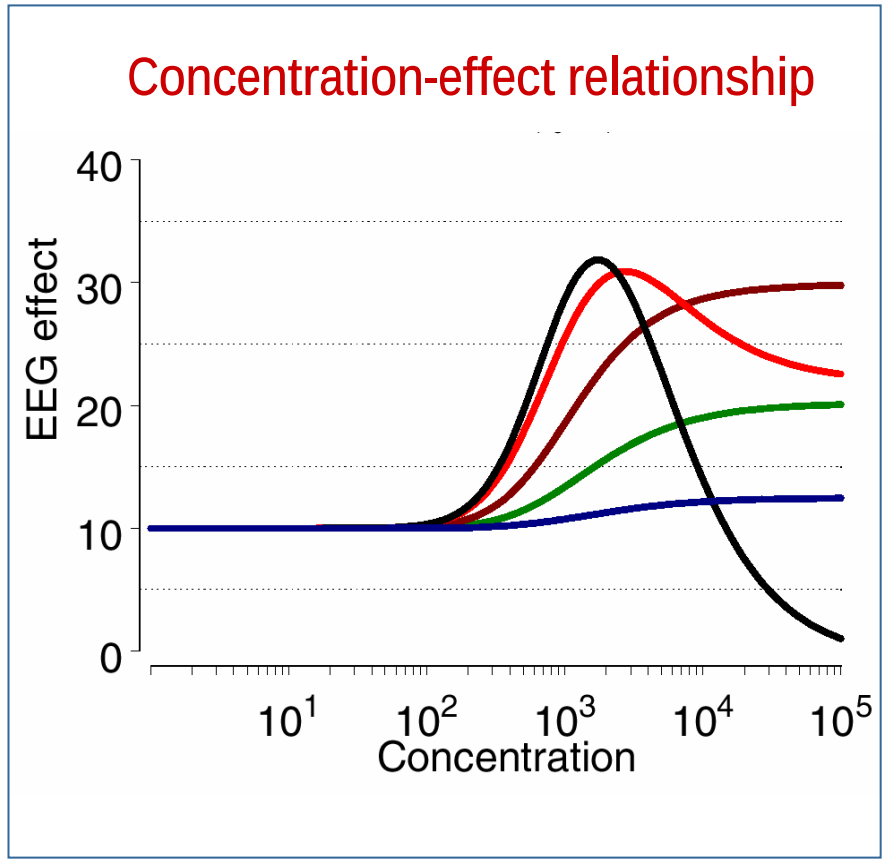


$$Stimulus = S(C) = \left[\frac{e_{PD} \cdot C_e}{C_e + K_{PD}} \right]$$

$$E = f(S) = E_{top} - a(S^d - b)^2$$

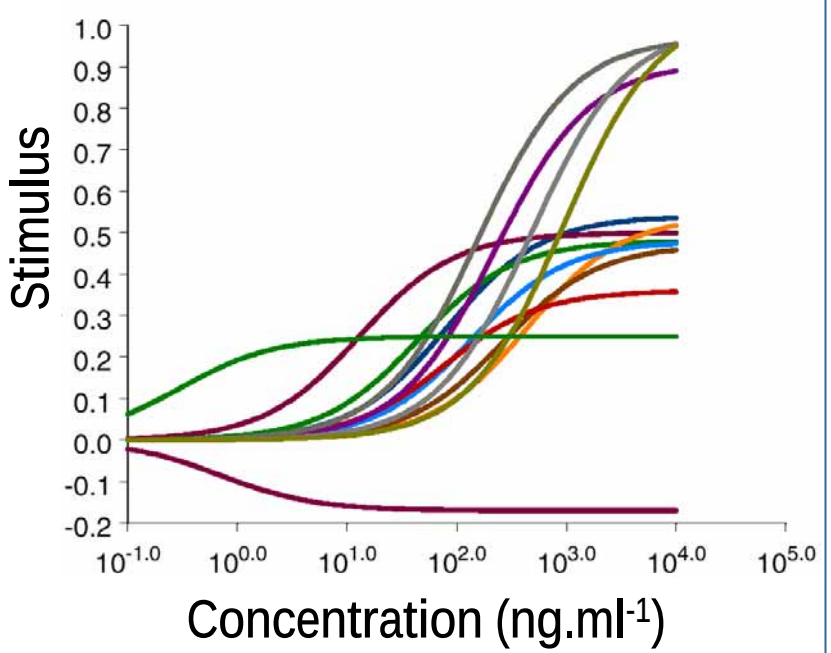
Model predicts monophasic concentration effect relationships for partial agonists



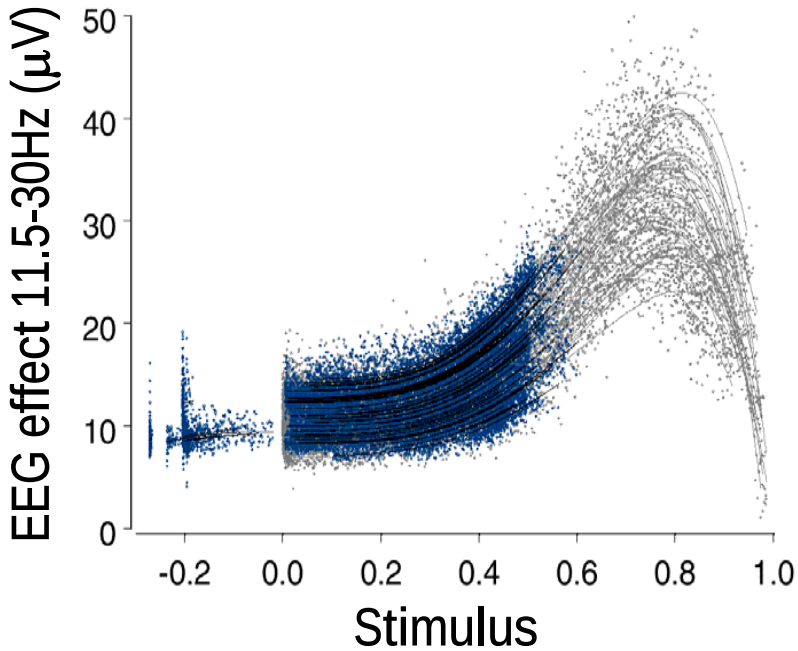


Benzodiazepines are partial agonists at the $GABA_A$ receptor in vivo

Drug-receptor interaction

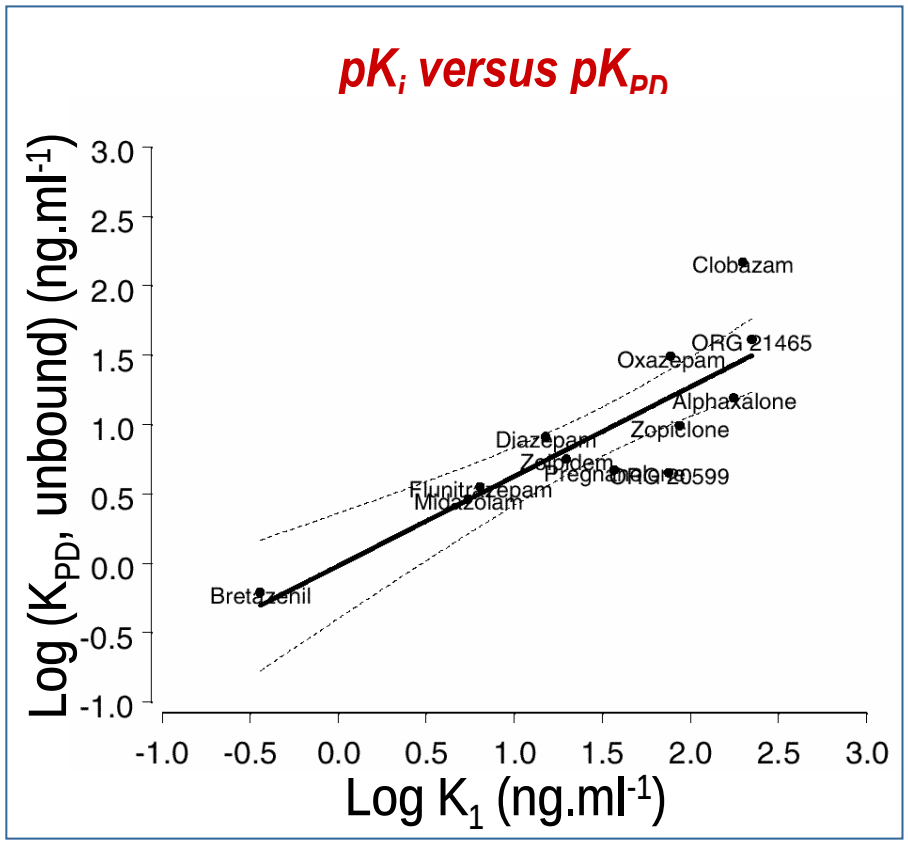


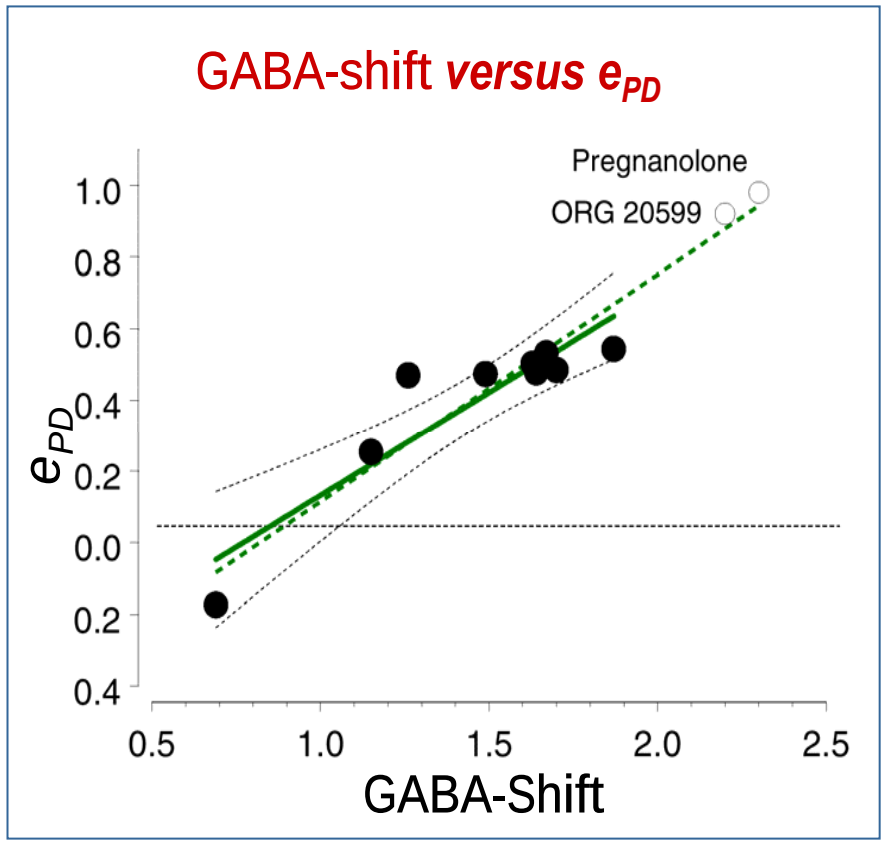
Stimulus-response relationship



From: Visser ***et al***., J. Pharmacol. Exp. Ther. 304: 88-101 (2003)

Mechanism-based PK-PD model allows prediction of potency and intrinsic efficacy





From: Visser ***et al.***, J. Pharmacol. Exp. Ther. 304: 88-101 (2003)

Application of receptor theory in PK-PD modeling is generally feasible

- A_1 adenosine receptor agonists
- Synthetic μ opioid receptor agonists
- 5-HT_{1A} serotonin receptor agonists
- $GABA_A$ receptor agonists
- Beta receptor antagonists
- hERG channel ligands
- ….
- ….

Application of receptor theory in PK-PD modeling challenges

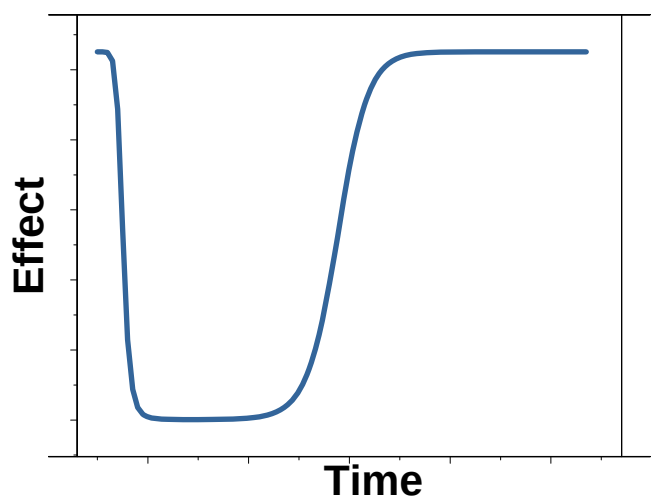
- Kinetics of receptor association and dissociation
- Modeling of "constitutive activity" and "inverse agonism"
- Modeling of "allosteric modulation"
- Modeling of the role of "receptor subunit composition"
  - Interspecies extrapolation
  - Intra- and inter-individual variation

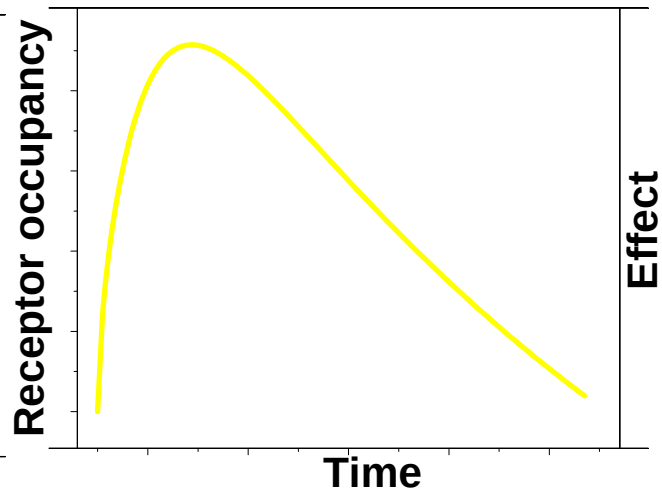
Implementing receptor theory in PK-PD modeling

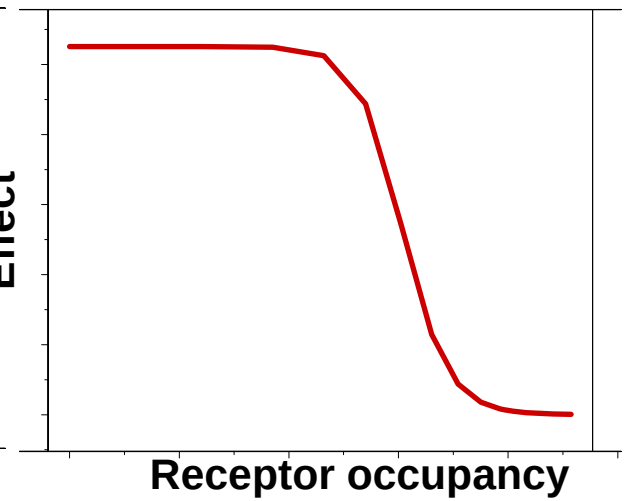
Kinetics of drug action

Kinetics of drug-action: receptor kinetics and transducer function

Time-course of drug effect = Receptor kinetics + Transducer Function



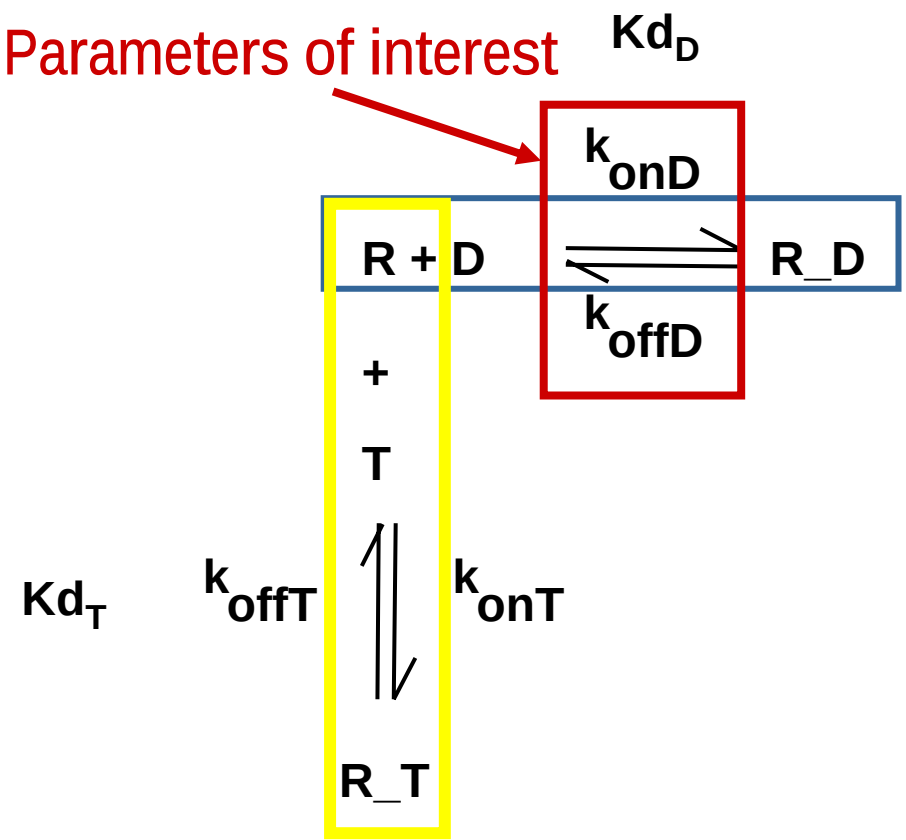


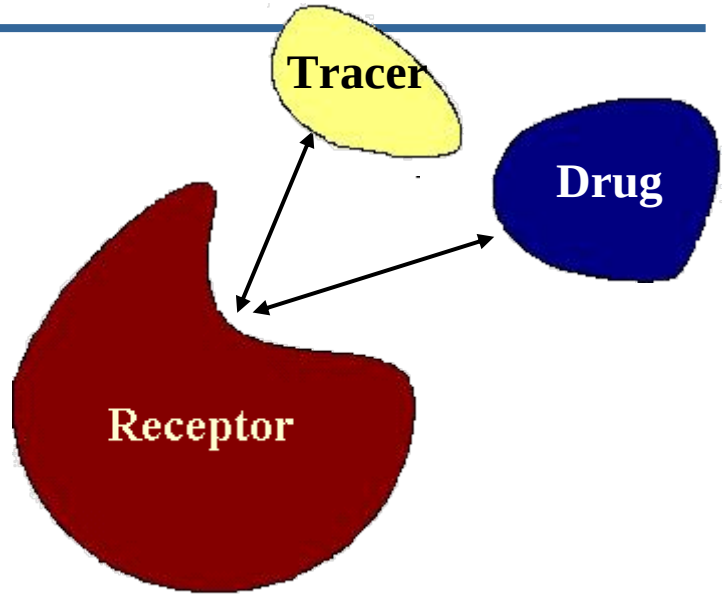


How to distinguish receptor kinetics from the transducer function?

- Two-stage approach
  - Estimate the receptor kinetics independently
    - ***In vitro*** receptor binding experiment
    - Measuring the concentration in the biophase
  - Fix receptor kinetics and estimate transducer function
- Simultaneous approach
  - Collect detailed data on pharmacology
    - Different doses and/or infusion scheme's
    - Combine data from compounds acting on the same system
      - Full and partial agonist, agonists and antagonists, etc.

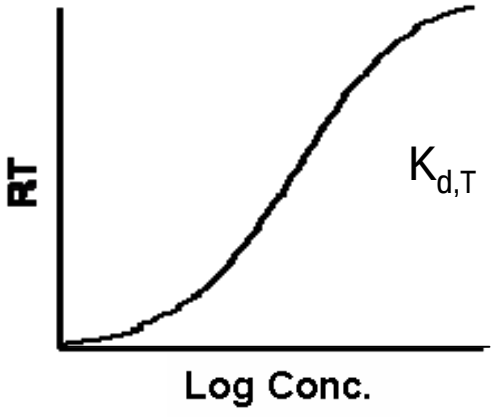
Estimating receptor kinetics in vitro using competition with a tracer



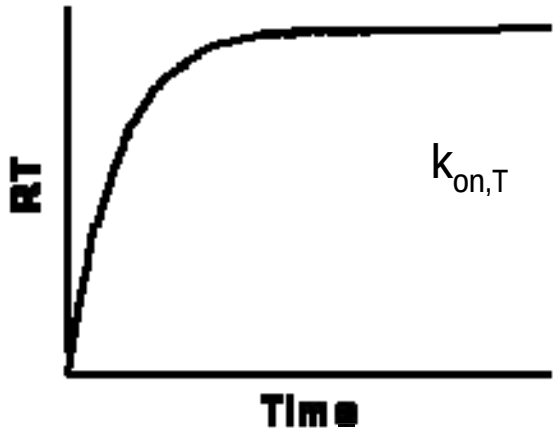


Kd_D (Kd drug)=k_{offD}/k_{onD}
Kd_T (Kd tracer)= =k_{offT}/k_{onT}
R: target
D: drug
T: tracer
RD: target-drug complex
RT: target-tracer complex

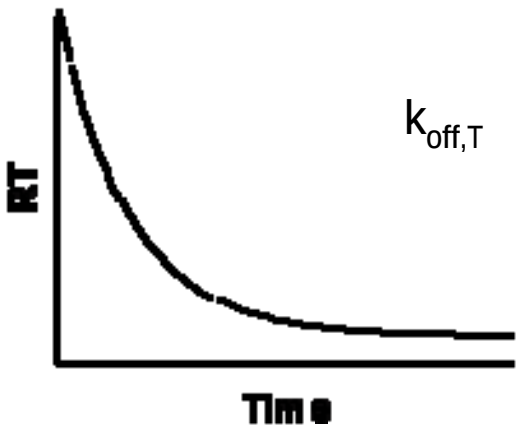
Estimating receptor kinetics in vitro
experimental approach



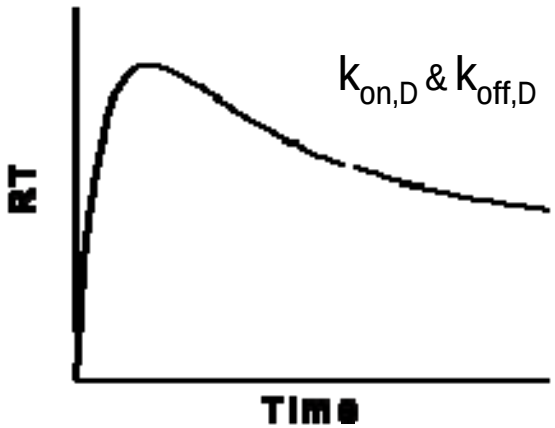
Equilibrium experiment



Association experiment



Dissociation experiment



Competitive binding experiment

Estimating receptor kinetics in vitro
model structure

Stuctural model:

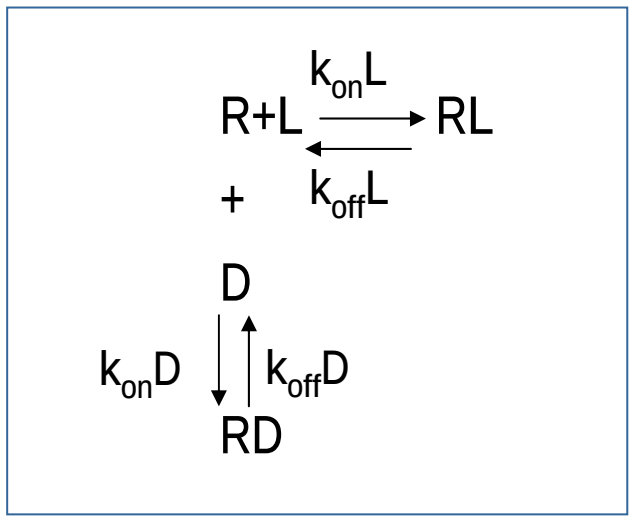
CL=concentration ligand; CD=concentration drug
Assumption: CL and CD in excess

$DADT(1)= k_{on}L*A(2)*L-A(1)*k_{off}L$; RL
$DADT(2)=-(k_{on}L*CL+k_{on}D*CD)*A(2)+A(1)*k_{off}L+A(3)*k_{off}D$; free R
$DADT(3)= k_{on}D*A(2)*CD-A(3)*k_{off}D$; RD

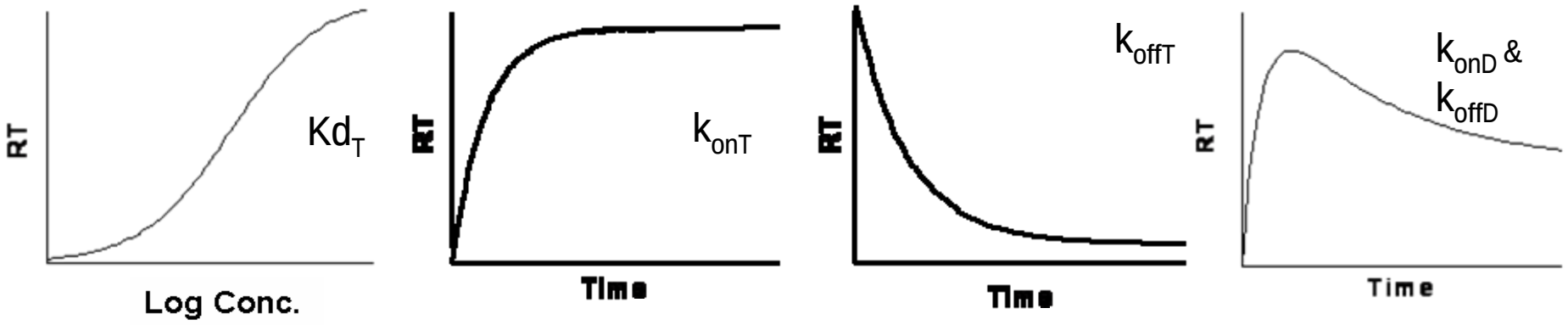
Association: IPRED= A(1)
Dissociation: IPRED= A(3)
Equilibrium: IPRED= $B_{max}*CL/(K_dL+CL)$

Stochastic model:

Between experiment variability on B_{max}
Proportional residual error



Estimating receptor kinetics in vitro
optimal design

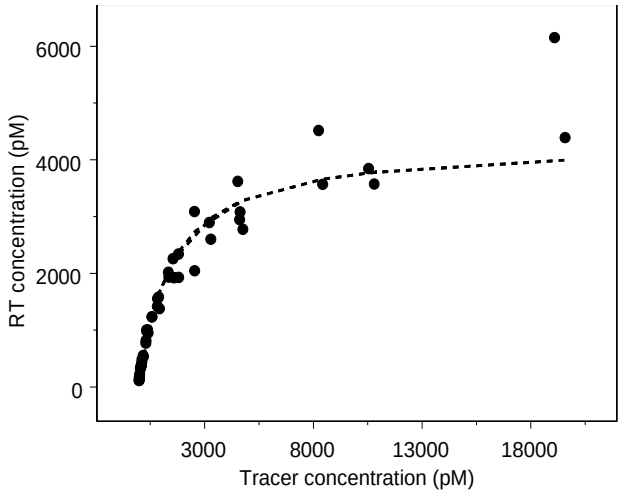


Equilibrium exp. Association exp. Dissociation exp. Competitive binding exp.

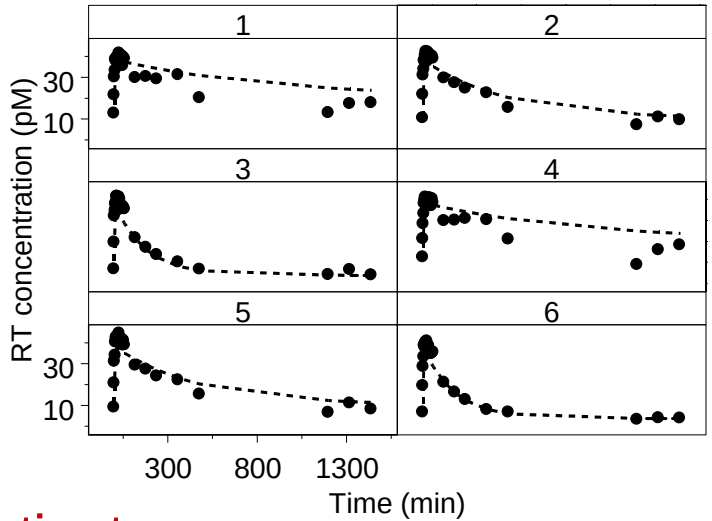
- All rate constants can be identified using equilibrium and competitive binding experiments
- Repeat competitive binding experiments for at least 3 drug concentrations
  - For the simulated compounds at least 10 measurements in the first hour are required

Estimating receptor kinetics in vitro
application to a slow-offset drug

Equilibrium experiments



Competitive binding experiments

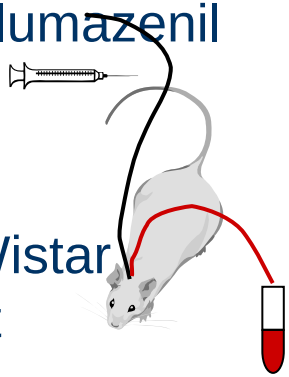


Parameter estimates

Parameter	equilibrium + competitive binding exp.	equilibrium + competitive binding + association exp.
k_{offT} (1/min)	0.175	0.159
KdT (pM)	1450	1450
k_{off} drug	0.000569	0.000569
Kd drug (pM)	51.3	51.3

Estimating receptor kinetics in vivo using biophase concentration data

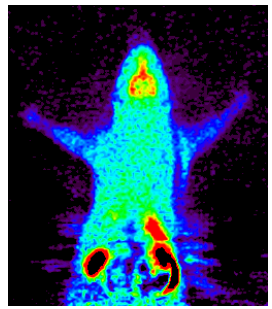
intravenous saturating injection of [^{11}C]Flumazenil



male Wistar rat

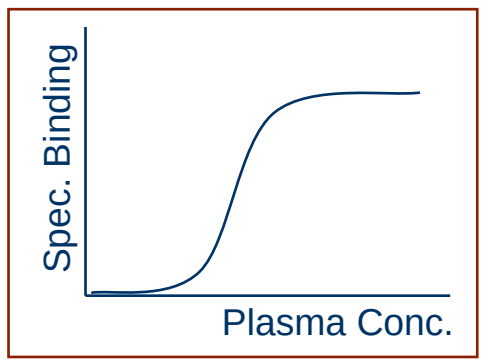
arterial blood sampling

scanning under anaesthesia



Flumazenil in brain with PET-scanner

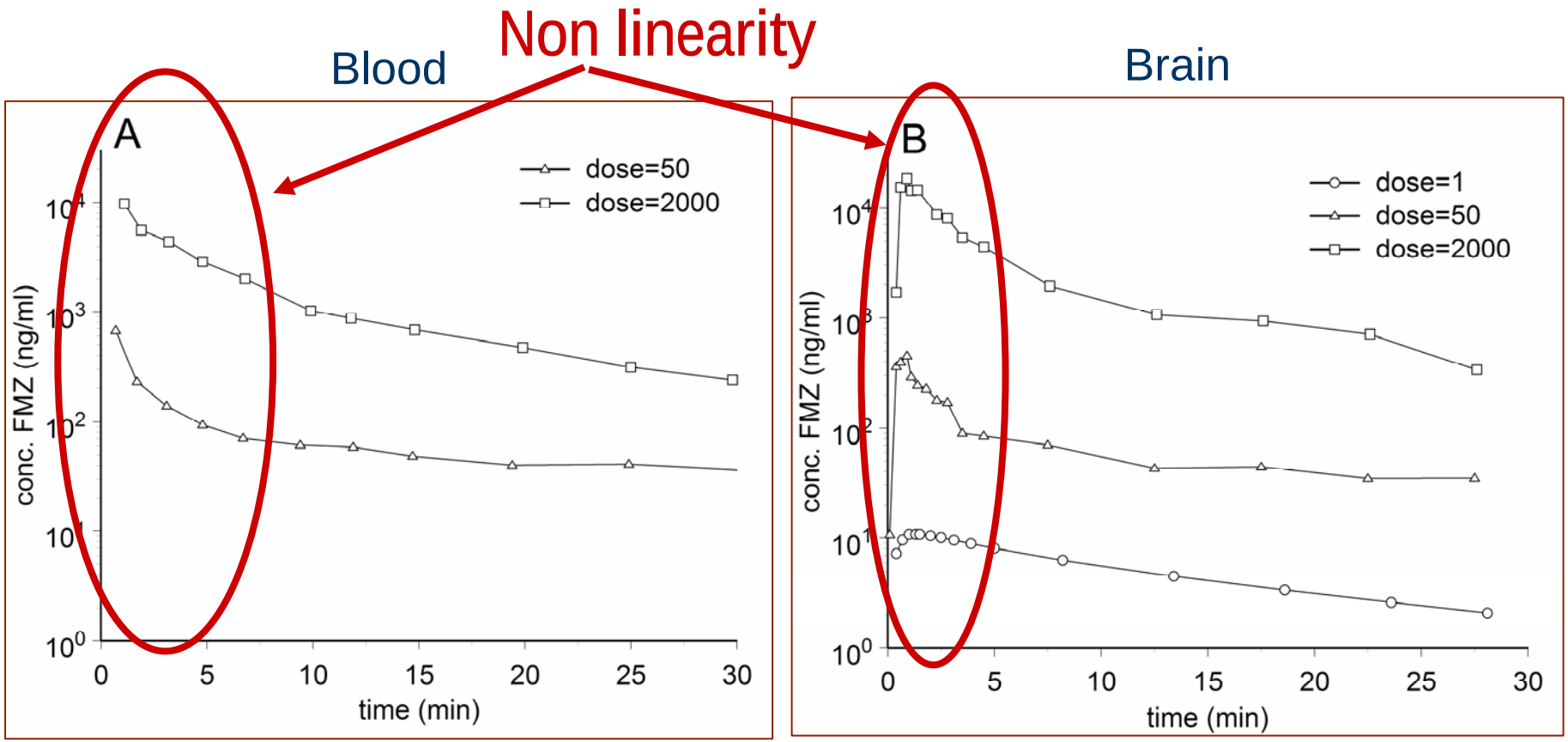
data analysis (NONMEM)



HPLC-UV analysis of Flumazenil in blood

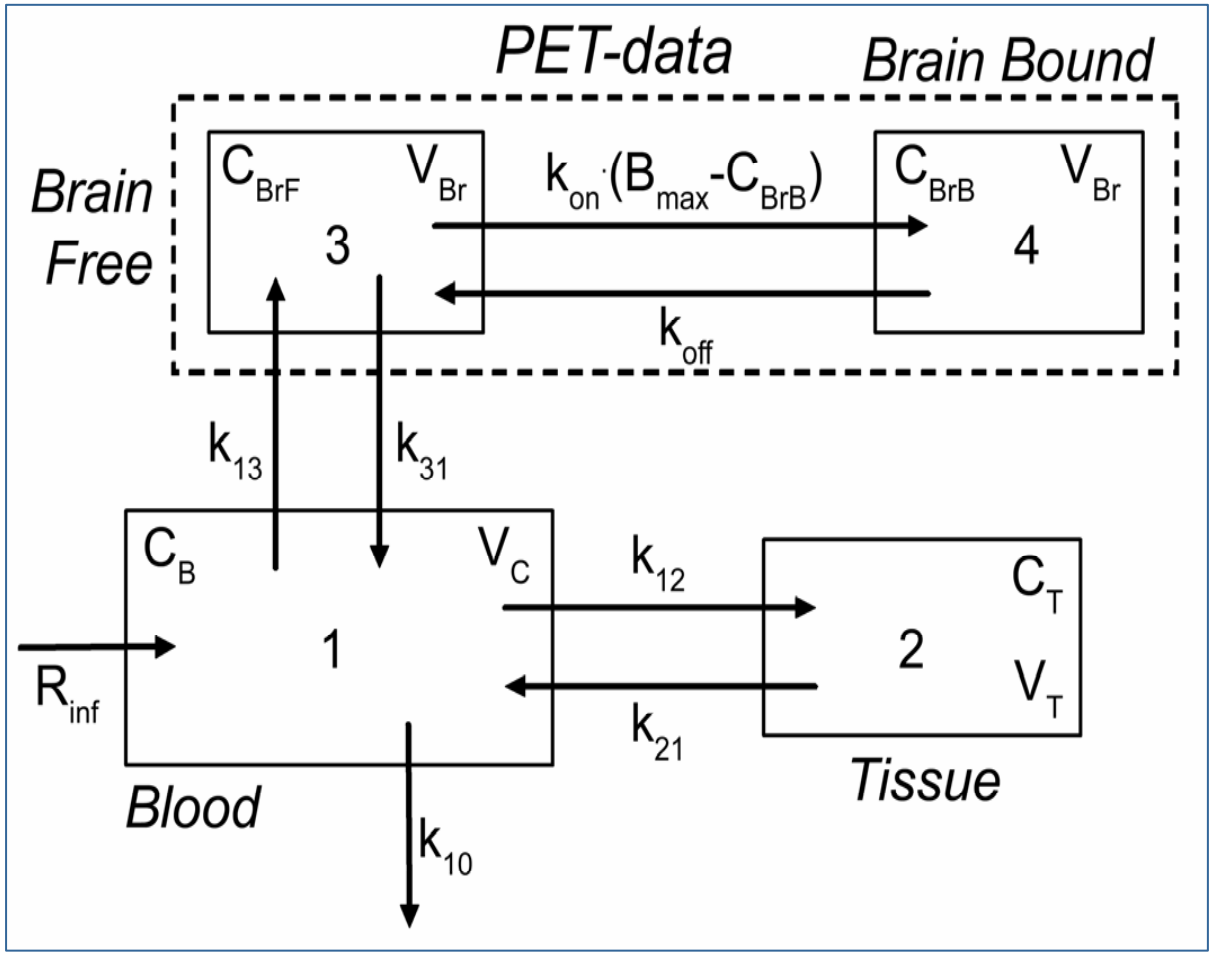
LC Liefaard ***et al. Mol. Imaging Biol.*** 2005;7(6):411-421

Estimating receptor kinetics of flumazenil in rat brain in vivo



LC Liefaard ***et al. Mol. Imaging Biol.*** 2005;7(6):411-421

Pharmacokinetic model for estimation of flumazenil receptor kinetics in vivo



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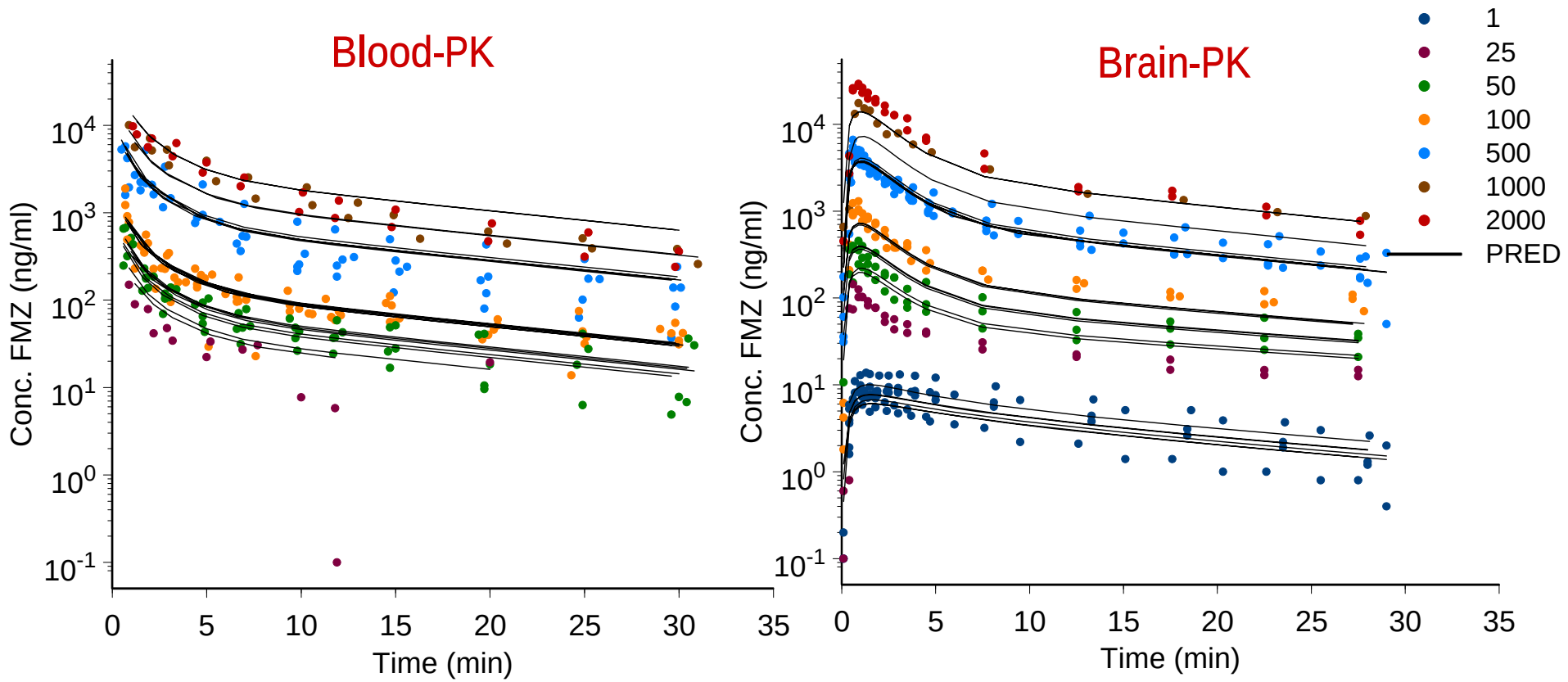
Pharmacokinetic model for estimation of flumazenil receptor kinetics in vivo



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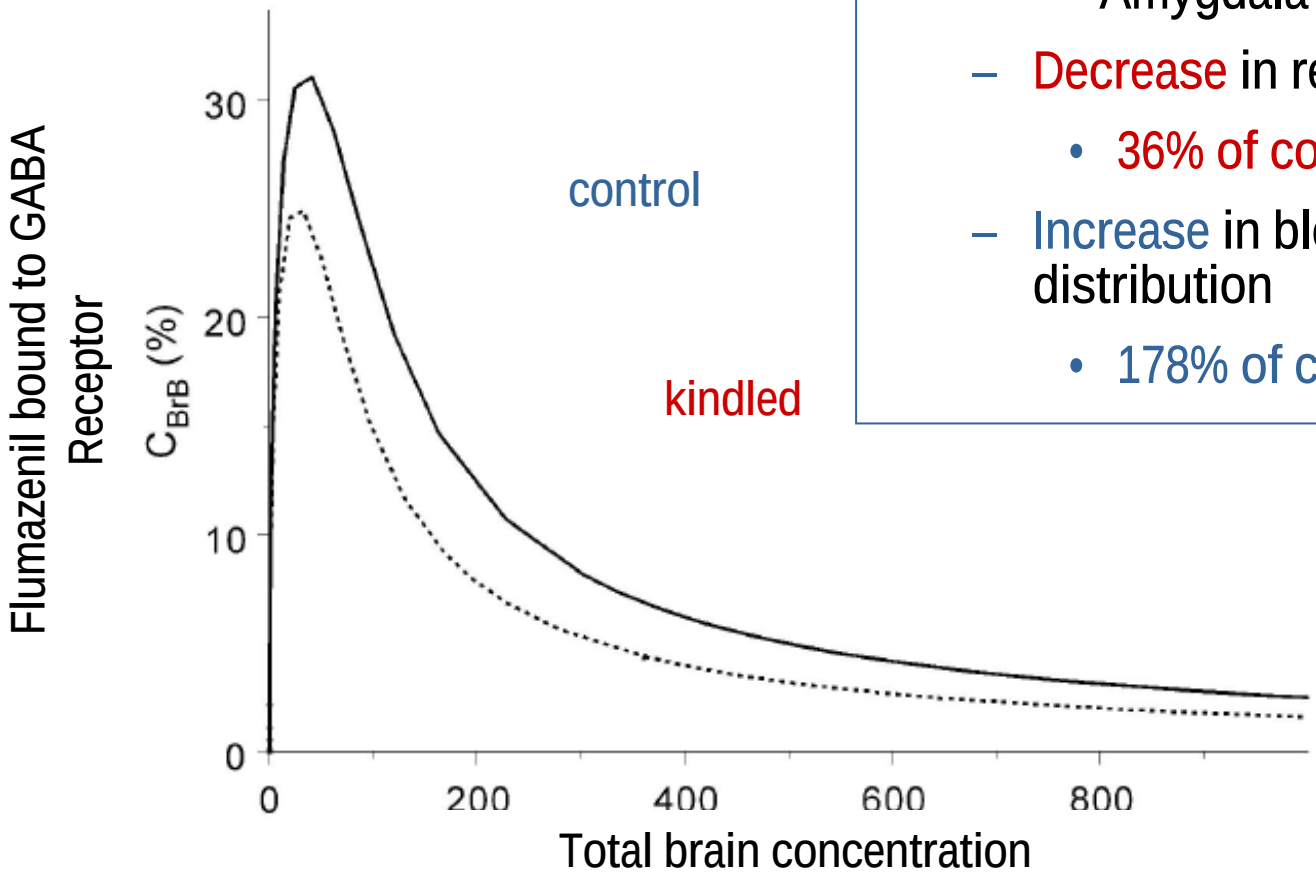
Effect of amygdala kindling on blood-brain transport and receptor kinetics



Amygdala kindling:

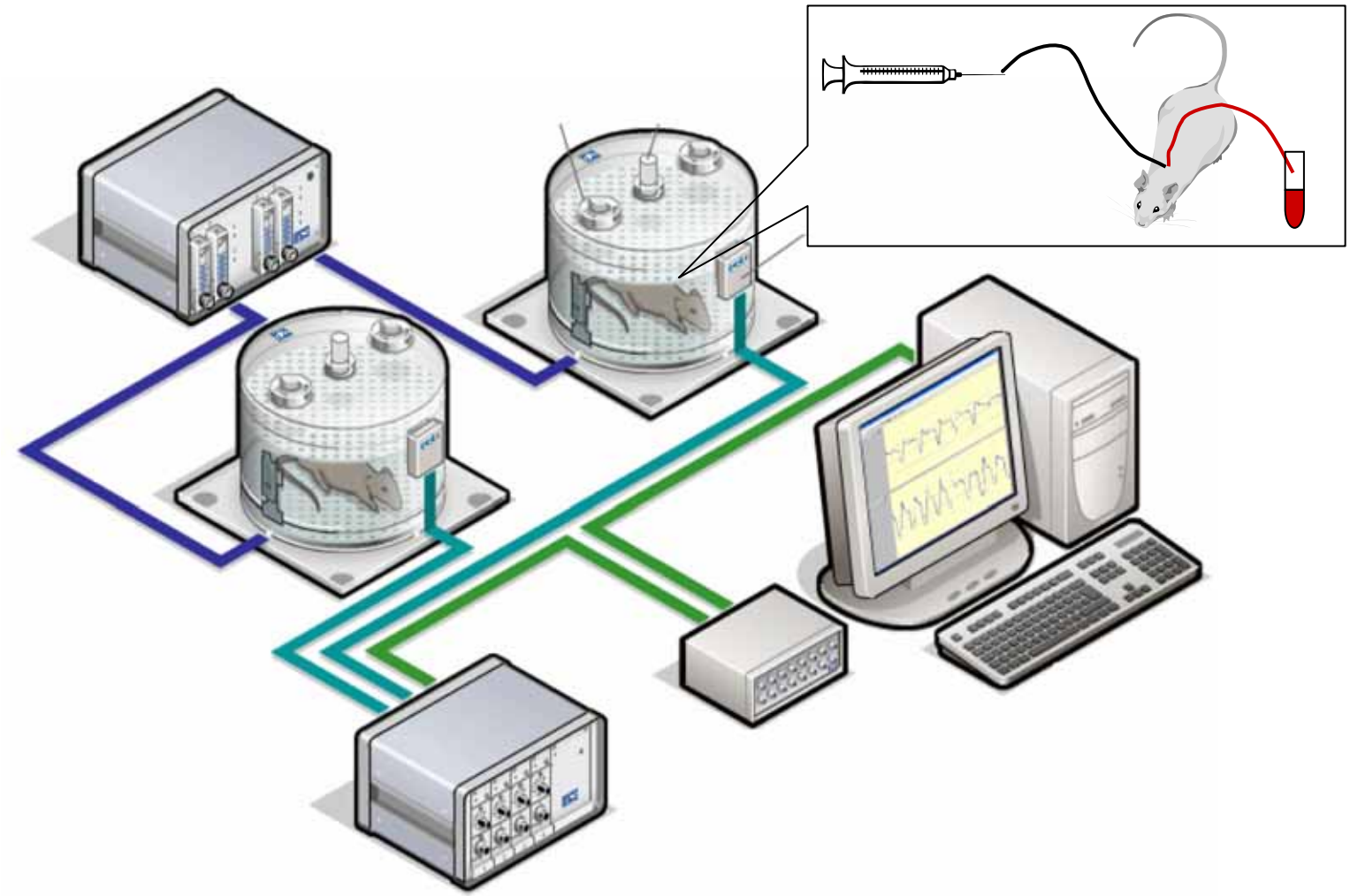
- Decrease in receptor capacity
  - 36% of control rats
- Increase in blood-brain distribution
  - 178% of control rats

LC Liefaard ***et al. Epilepsia*** 2008;accepted

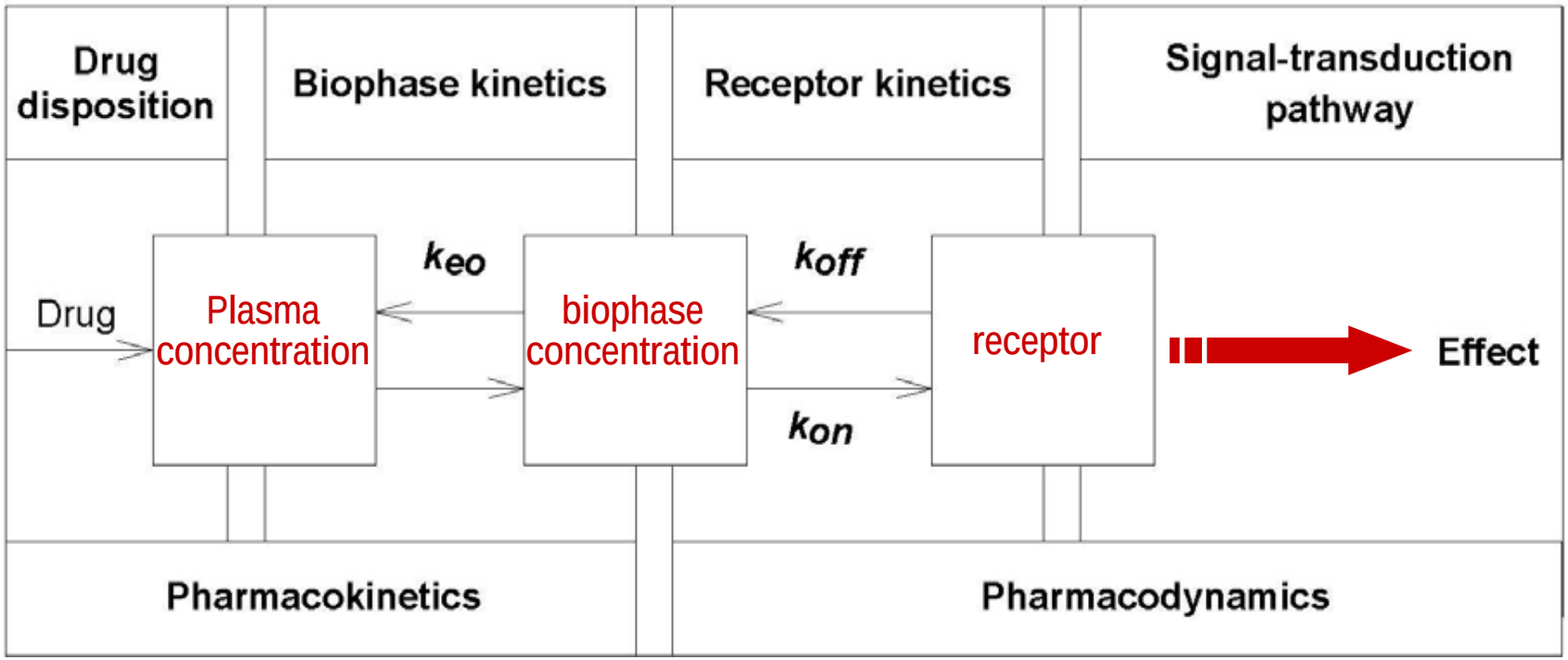
Simultaneous estimation of receptor kinetics and transducer function: opioids

- Natural and (semi-)synthetic opioids are effective analgesics
- Potentially life-threatening respiratory depression is a major concern
- Design of novel opioids with optimized efficacy-safety
  - Partial agonism as the basis for improved selectivity of action

Whole body plethysmography for monitoring of respiratory depression in rats



PK-PD correlation of semi-synthetic opioids
mechanisms of hysteresis



Yassen et al., (2006) J. Pharmacol. Exp. Ther. 319: 682-692.

Modeling of hysteresis in the effects of fentanyl and buprenorphine

(a) Biophase distribution model

$$\frac{dC_e}{dt} = k_{e0} \cdot (C_p - C_e)$$

(b) Receptor association/dissociation model

$$\frac{dC_pR}{dt} = k_{on} * C_p * (1 - C_pR) - k_{off} * C_pR$$

(c) Combined model (a + b)

$$\frac{dC_eR}{dt} = k_{on} * C_e * (1 - C_eR) - k_{off} * C_eR$$

Yassen et al., (2006) J. Pharmacol. Exp. Ther. 319: 682-692.

Modeling of the concentration-effect relations of fentanyl and buprenorphine

- Sigmoid E_{max} model (Hill equation)

$$E = 1 - \frac{\alpha \cdot C^n}{EC_{50}^n + C^n}$$

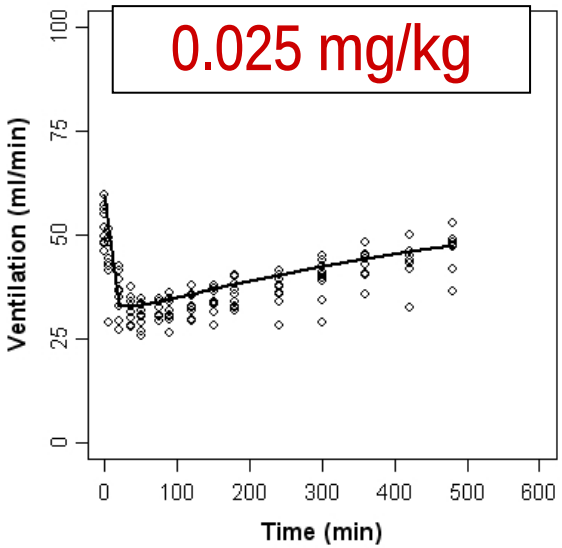
- Receptor model with linear transduction

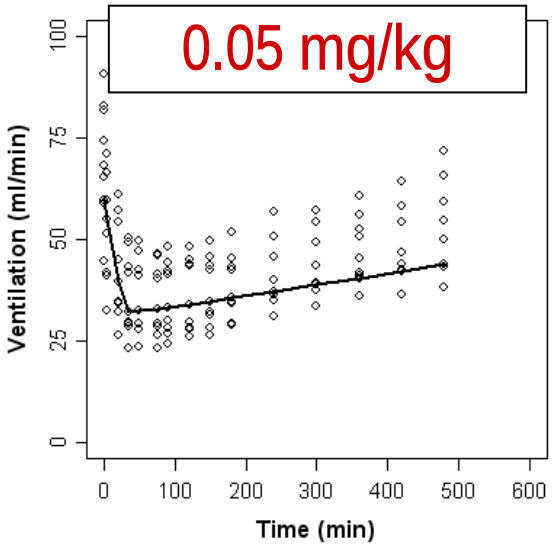
$$\frac{[C_e R]}{[R_{tot}]} = \frac{C_e}{K_D + C_e}$$

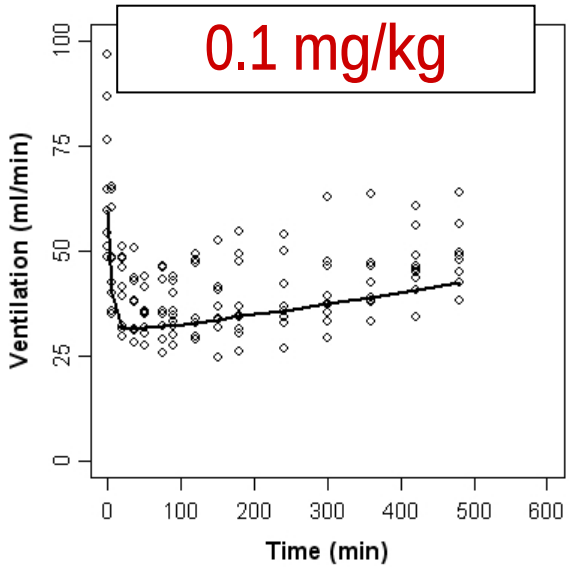
$$E = E_0 \cdot \left(1 - \alpha \cdot \frac{[C_e R]}{[R_{tot}]}\right)$$

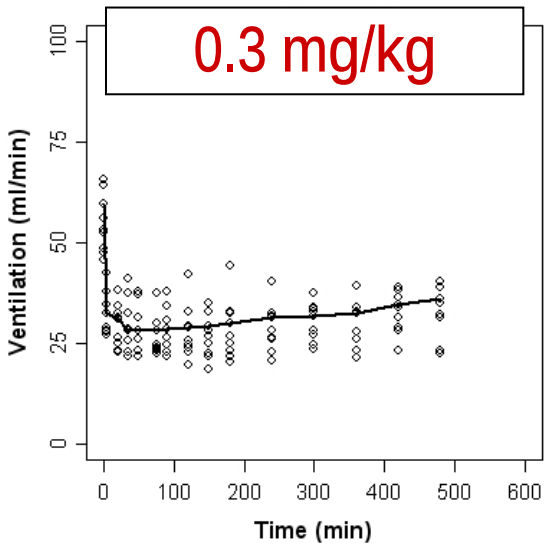
Yassen et al., (2006) J. Pharmacol. Exp. Ther. 319: 682-692.

Time course of respiratory depression in rats following buprenorphine







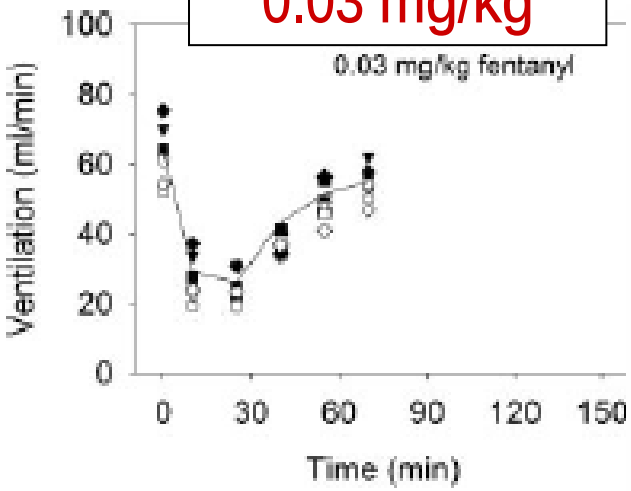


- Detailed dataset with wide dose range
- Slow receptor dissociation?
- Partial agonist?

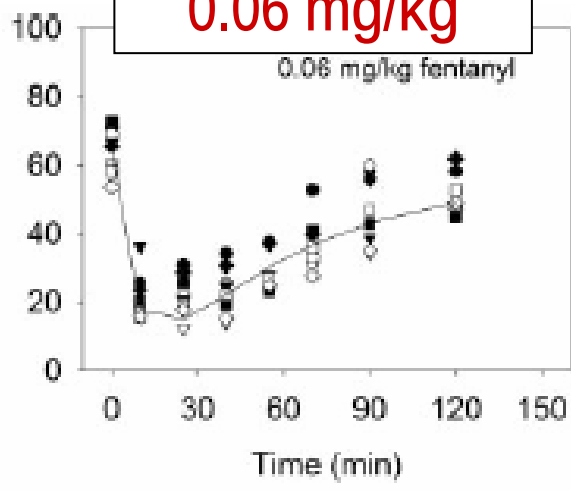
Yassen et al., (2006) J. Pharmacol. Exp. Ther. 319: 682-692.

Time course of respiratory depression in rats following fentanyl

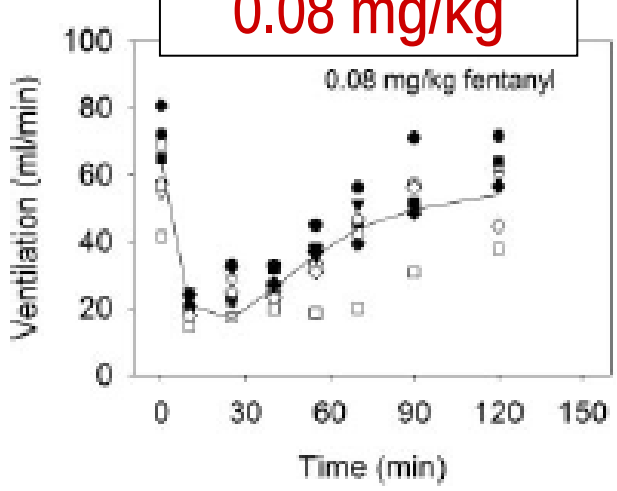
0.03 mg/kg



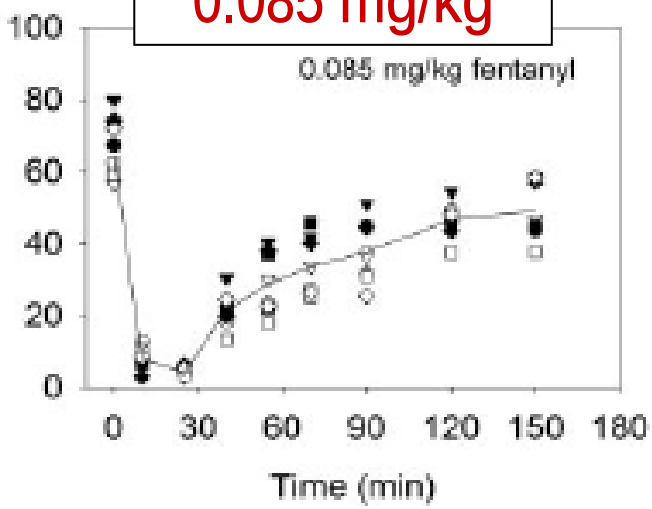
0.06 mg/kg



0.08 mg/kg



0.085 mg/kg



- Fast receptor association/dissociation
- Full agonist?

Yassen et al., (2006) J. Pharmacol. Exp. Ther. 319: 682-692.

Mechanism-based model for respiratory depression parameter estimates

	Fentanyl	Buprenorphine
k_{e0}, min^{-1}	0.44 (-)	0.035 (79%)
$T_{½,keO}$, min	1.6	19.9
k_{on}, $ml.ng^{-1}.min^{-1}$	(> 100)	0.572 (-)
k_{off}, min^{-1}	(> 100)	0.090 (75%)
$T_{½,koff}$, min	(~ 0)	7.8
K_D, $ng.ml^{-1}$	n.a.	0.16
EC_{50}, $ng.ml^{-1}$	4.83 (84%)	n.a.
α	~1	0.48 (14%)
Hill factor	1.15 (-)	n.a.

Yassen et al., (2006) J. Pharmacol. Exp. Ther. 319: 682-692.

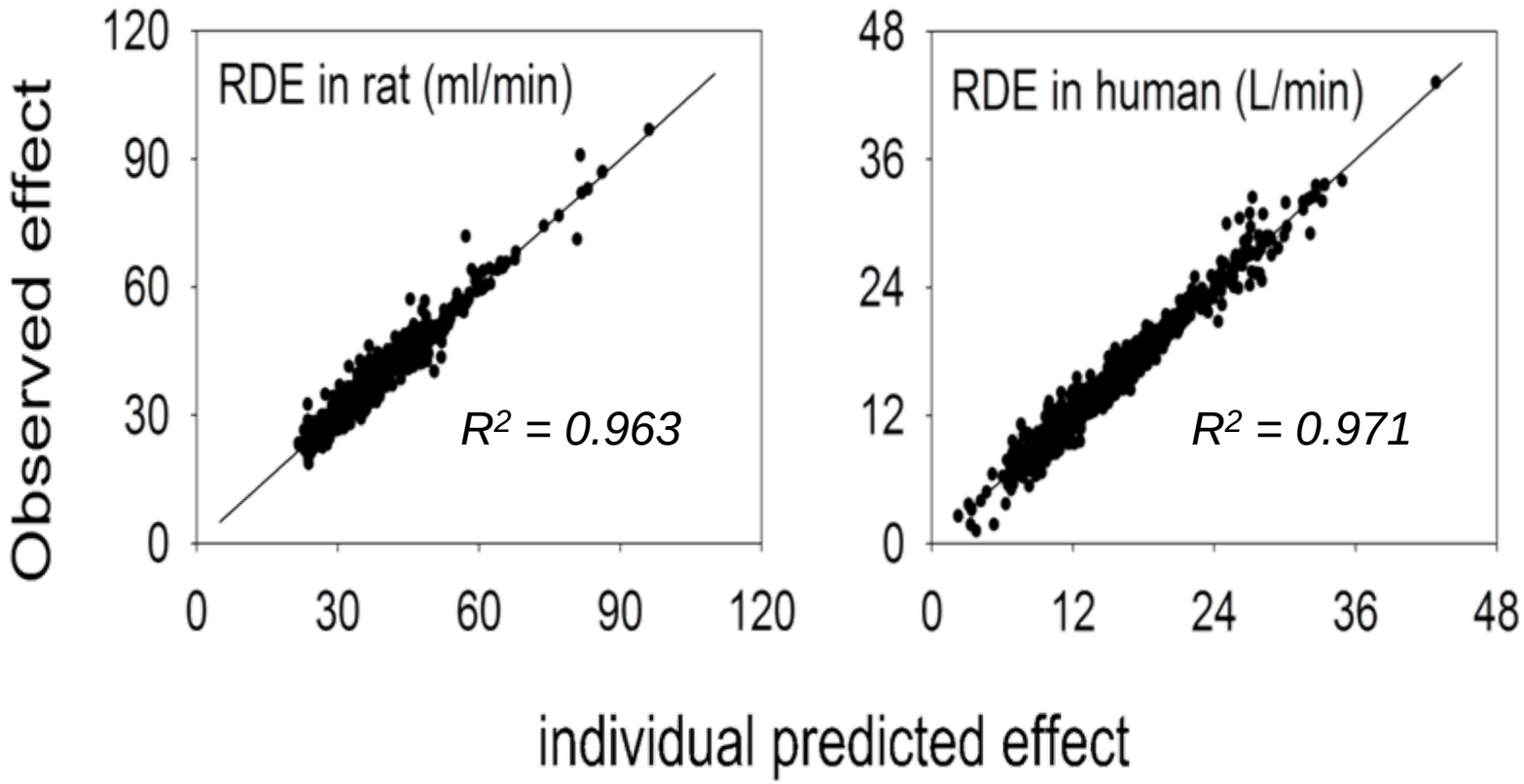
Animal to human extrapolation of the pharmacodynamics of buprenorphine

- Simultaneous analysis of the effects in rats and humans
  - Respiratory depression
  - Antinociception
- No scaling of receptor association-dissociation kinetics (drug-specific properties)
- Allometric scaling of biophase distribution kinetics

$$k_{e0} = a \cdot WT^{b}$$

Yassen et al., (2007) Clin. Pharmacokin. 46:433-447.

Animal to human extrapolation of the pharmacodynamics of buprenorphine



Yassen et al., (2007) Clin. Pharmacokin. 46: 433-447.

Animal to human extrapolation of the pharmacodynamics of buprenorphine

	Antinociception	Respiratory depression
Drug specific parameters		
k_{on}, ml.ng^{-1}.min^{-1}	0.015 (18.3)	0.23 (15.8)
k_{off}, min^{-1}	0.053 (23.1)	0.014 (27.7)
K_D, nM	7.5	0.13
α	n.e.	0.52
System specific parameter		
$k_{e0} = a.WT^b$		
a, min^{-1}	0.0303 (11.3)	
b	- 0.28 (9.6)	

Yassen et al., (2007) Clin. Pharmacokin. 46: 433-447.

Implementing receptor theory in PK-PD modeling

Concluding remarks

Implementing receptor theory in PK-PD modeling conclusions

- Estimation of receptor theory PK-PD models requires detailed information on pharmacology
- Data should allow to distinguish drug-specific and system-specific parameters
  - Combine ***in vitro*** and ***in vivo*** data
  - Evaluate different dose levels and/or infusion scheme's
  - Combine data from compounds acting on the same system