Supplementary materials: Development of a Region-Specific Brain Physiologically-Based Pharmacokinetic Model to Assess Hippocampus and Frontal-Cortex Pharmacokinetics

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1. Whole-body physiologically based pharmacokinetic (PBPK) CNS model

Well-stirred tissues

$$\frac{dC_T}{dt} = \left[\frac{1}{V_T} \times Q_T \times C_{AR}\right] - \left[\frac{1}{V_T} \times Q_T \times \left(\frac{C_T}{f_{up} \times K_p} \times R_b\right)\right] \quad (1)$$

where C_T is the drug concentration of the respective tissues, t is for time, Q_T is the blood flow rate of the tissue, C_{AR} is the arterial drug input, V_T is the volume of the respective tissue compartment, f_{up} is the fraction unbound of drug in plasma, K_p is the tissue-to-plasma partition coefficient and R_b is the blood-to-plasma ratio of the drug.

Brain:

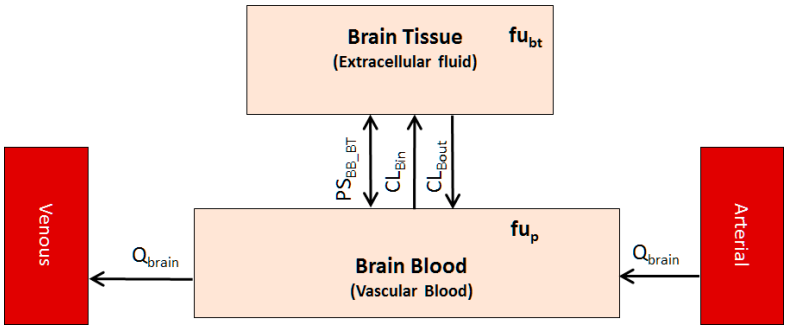

Figure S1. CNS PBPK brain model. Q: blood flow; PS: permeability surface-area; BB: intravascular blood; BT: brain tissue; fu: drug fraction unbound.

$$\frac{dC_{bb}}{dt} = Q_{brain}(C_{arterial} - C_{bb}) + \left(PS_{BB}C_{bt}fu_b - PS_{BB}C_{bb}fu_p\right) \quad (2)$$

where C_{bb} is the drug concentration in the brain blood (brain vascular blood), t is for time, Q_{brain} is the blood flow rate to the brain, $C_{arterial}$ is the arterial drug input, fu_p is the fraction unbound of drug in plasma and brain (fu_p), PS is the bidirectional passive permeability-surface area product of BBB and CL_{Bin} and CL_{Bout} are the active clearance into and out of the brain, respectively.

1.1. Compound parameters

Unless otherwise stated, all data contained within the tables below are applied to the rat CNS PBPK model. For a complete description of model parameters, estimation methods (where applied) and references, please see Badhan *et al* (2014) [1].

Table S1. *In-vitro* permeability data.

	Parental cells [a]
	P_{app}

	cm/s (x10^{-6})	
	AB	**BA**
Benzypenicillin	4.35	3.17
Buspirone	34.25	33.6
Caffeine	27.0	29.7
Carbamazepine	3.45	34.5
Diazepam	37.3	36.8
Midalzolam	34.8	35.5
Phenytoin	20.94	31.7
Sertraline	2.27	1.61
Thiopental	31.2	30.6
Zolpidem	35.6	35.4

[a] Data obtained from [2,3]

Table S2. Model predicted ***versus*** literature reported ***in situ*** permeabilities.

	Permeability Clearance		**In Situ Permeability**
	mL/h		**mL/h**
	PS_{BB_BT}	**PS_{BT_BB}**	
Benzypenicillin	4.3	3	0.97 [4]
Buspirone	33.3	32.6	
Caffeine	26.3	28.2	95 ±33.7 [5–8]
Carbamazepine	33.6	33.5	116 [9]
Diazepam	36.3	35.8	351 ±254 [5,9,10]
Midalzolam	33.9	34.5	459 [9]
Phenytoin	25.4	30.8	36.7 ± 21 [8,9,11]
Sertraline	2.2	1.6	129 [12]
Thiopental	30.4	29.8	-
Zolpidem	34.7	34	-

Table S3. Physicochemical parameters used to calculate partition coefficients.

	Physicochemical parameters [a]	
	pKa	**LogP**
Benzypenicillin	3.55 [b]	2.74 [c]
Buspirone	7.62	1.95 [d]
Caffeine	14	0.92 [e]
Carbamazepine	15.96	2.1
Diazepam	3.4 [c]	2.82 [f]
Midalzolam	6.2	3.89
Phenytoin	8.3 [g]	2.5
Sertraline	9.16 [h]	5.1
Thiopental	7.55 [f]	2.85 [b]
Zolpidem	6.2	1.2

All partition coefficient were subsequently calculated using Rogers and Rowlands mechanistic approaches [13,14].

[a.] Unless otherwise stated, calculated using ChemAxon
[b.] Hansch *et al* (1995) [15]
[c.] Merck Index (2001) [16]
[d.] Ullrich and Rumrich (1992) [17]
[e.] Martin *et al* (1969) [18]
[f.] Sangster (1994) [19]
[g.] McLure *et al* (2000) [20]
[h.] Deak *et al* (2006) [21].

Table S4. Protein binding and metabolic clearance.

	Protein Binding [a]			**Metabolic Clearance**
	Plasma	Brain	CSF	Rat [b]
				CLint, **in vivo**
	fu$_{plasma}$	**fu**$_{brain}$	**fu**$_{CSF}$	mL/min/kg
Benzypenicillin	0.649	2.26	0.998	na
Buspirone	0.45	0.137	0.996	95.34
Caffeine	0.917	0.697	1	0.70
Carbamazepine	0.385	0.17	0.995	0.37
Diazepam	0.211	0.0426	0.989	0.88
Midalzolam	0.045	0.0431	0.94	75.66
Phenytoin	0.302	0.0967	0.993	0.56
Sertraline	0.0347	0.00038	0.923	158.01 [c]
Thiopental	0.202	0.244	0.988	na
Zolpidem	0.267	0.265	0.992	7.47

[a.] Taken from Kodaira *et al* (2011) [22].
[b.] Unless otherwise indicated, intrinsic *in-vivo* clearance was calculated based on a well-stirred liver model assuming average hepatic blood flow (Q_H, 55 mL/min/kg). Blood clearance and unbound fraction in blood were determined using the blood:plasma ratio (R_b) or by assuming a value of 1 for basic and neutral drugs and 0.55 for acidic drugs.
[c.] Calculated from Ronfield *et al* (1997) [23]

Table S5. Renal Clearance.

Compound	**Rat**
	CL_R ml/min/kg
Benzypenicillin	10.22 [a]
Buspirone	na
Caffeine	0.021 [b]
Carbamazepine	na
Diazepam	na
Midalzolam	na
Phenytoin	na
Sertraline	na
Thiopental	na

Zolpidem	na

Renal clearance in rats (CL_R) was calculated based on glomerular filtration rate (GFR) ratio approach as described by Lin (1998) [24]

[a.] Taken from Scavone *et al* (1989 [25], 1997 [26]) and Thompson *et al* (1996) [27]

[b.] Taken from Birkett and Miners (1991) [28].

2. Regional brain PBPK sub-model

Intercranial blood ('brain blood'):

$$\begin{aligned}\frac{dC_{bb}}{dt} = {} & Q_{brain}(C_{art} - C_{bb}) + \left(PS_{FC\_BB}C_{fc}fu_{fc} - PS_{BB\_FC}C_{bb}fu_{p}\right) \\ & + \left(PS_{BT\_BB}C_{bt}fu_{bt} - PS_{BB\_BT}C_{bb}fu_{p}\right) + CL_{Bout}C_{bt}fu_{bt} \\ & - CL_{Bin}C_{bb}fu_{p} + \left(PS_{HC\_BB}C_{hc}fu_{hc} - PS_{BB\_HC}C_{bb}fu_{p}\right) \\ & + Q_{CSink}C_{csf}fu_{csf}\end{aligned} \quad (3)$$

where the subscripts *art*, *bb*, *bt*, *csf*, *hc*, *fc*, *p*, and *Csink* represent arterial blood, brain blood, brain tissue, cerebral spinal fluid, hippocampus, frontal cortex, plasma and CSF absorption, respectively; *Q* is blood or CSF flow; *CL* is transporter clearance, respectively; *PS* is the passive permeability-surface area product of BBB, BCSFB, blood brain to hippocampus (and *vice versa*), and blood brain to frontal cortex (and *vice versa*), respectively; *fu* is fraction unbound.

Brain tissue (rest of brain tissue):

$$\begin{aligned}\frac{dC_{bt}}{dt} = {} & \left(PS_{BB\_BT}C_{bb}fu_{p} - PS_{BT\_BB}C_{bt}fu_{bt}\right) + CL_{Bin}C_{bb}fu_{p} - CL_{Bout}C_{bt}fu_{bt} \\ & + \left(PS_{FC_{BT}}C_{fc}fu_{fc} - PS_{BT_{FC}}C_{bt}fu_{bt}\right) - Q_{bulkBT_{CSF}}C_{bt}fu_{bt} \\ & + \left(PS_{HC_{BT}}C_{hc}fu_{hc} - PS_{BT_{HC}}C_{bt}fu_{bt}\right)\end{aligned} \quad (4)$$

where Q_{bulkBT_CSF} is the bulk flow from the brain tissue to the CSF.

Frontal cortex:

$$\begin{aligned}\frac{dC_{fc}}{dt} = {} & \left(PS_{BB\_FC}C_{bb}fu_{p} - PS_{FC\_BB}C_{fc}fu_{fc}\right) - Q_{bulkFC\_CSF}C_{fc}fu_{fc} \\ & + \left(PS_{BT\_FC}C_{bt}fu_{bt} - PS_{FC\_BT}C_{fc}fu_{fc}\right)\end{aligned} \quad (5)$$

where Q_{bulkFC_CSF} is the bulk flow from the frontal cortex to the CSF.

Hippocampus:

$$\begin{aligned}\frac{dC_{hc}}{dt} = {} & \left(PS_{HC\_BT}C_{bb}fu_{p} - PS_{BT\_HC}C_{hc}fu_{hc}\right) - Q_{bulkHC_{CSF}}C_{hc}fu_{hc} \\ & + \left(PS_{BB_{HC}}C_{bb}fu_{p} - PS_{HC_{BB}}C_{hc}fu_{hc}\right)\end{aligned} \quad (6)$$

where Q_{bulkHC_CSF} is the bulk flow from the hippocampus to the CSF.

CSF:

$$\begin{aligned}\frac{dC_{csf}}{dt} = {} & Q_{CSink}C_{csf}fu_{csf} + Q_{bulkBT_{CSF}}C_{bt}fu_{bt} + Q_{bulkFC\_CSF}C_{fc}fu_{fc} \\ & - Q_{CSink}C_{csf}fu_{csf}\end{aligned} \quad (7)$$

2.1. Compound specific data

Table S6. Physicochemical parameters for the human regional brain model.

	In-vitro permeability (cm/s x10^{-6})		Permeability clearance (mL/h) [b]		pKa	LogP	fu_{plasma}	fu_{brain}	fu_{CSF}	Rb	$CL_{int,in\text{-}vivo}$	CL_R
	$Papp_{AB}$	**$Papp_{BA}$**	**PS_{BB_BT}**	**PS_{BT_BB}**							**(mL/min/kg)**	
Carbamazepine	-	-	29818	33818	-	-	-	-	-	-	0.4	na
Phenytoin	-	-	22545	27418	-	-	-	-	-	-	0.47	na
Morphine	1.07[a]	1.06[a]	924	926	8.9[c]	0.89[d]	0.74[e]	0.45[f]	1[g]	1.02[f]	18	na

Data for carbamazepine and phenytoin can be found in supplementary materials section 1.1

[a] Obtained from [29]

[b] PS was calculated as described in Section 2.1 of the main manuscript. PS was subsequently applied to all regional brain compartments through correction for regional tissue weight (See Section 2.2 and assumption 8 of in the manuscript)

c obtained from [30]

d obtained from [31]

e obtained from [32]

f obtained from [33]

g assumed to be 1

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