Population PKPD Modeling of BACE1 Inhibitor-Induced Reduction in Aβ Levels in vivo.

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Introduction

Amyloid plaque formation in the brain is a hallmark neuropathological lesion in Alzheimer's disease (AD). The transmembrane aspartic acid protease BACE1 cleaves amyloid precursor protein (APP) to generate soluble APPβ. The remainder of APP in the plasma membrane, C99, is in turn cleaved by γ-secretase to form beta amyloid (Aβ). Aβ is a major component of plaque and small aggregates appear cytotoxic.

Purpose

In vivo, pharmacologically induced Aβ reduction is dependent on compound- and system-parameters, i.e. potency and Aβ clearance respectively. Preclinical PKPD modeling was applied

- to gain insight in the time-course between oral dose, plasma and brain exposure and inhibitory effect on Aβ in brain and CSF of novel BACE1 inhibitors, as well as system constants,
- to quantify the *in vivo* potency using population pharmacokinetic and pharmacodynamic (PKPD) modeling,
- to investigate the correlation between *in vitro* and *in vivo* potency.

In vivo results

In vivo our BACE1 inhibitors exhibited concentration- and time-dependent lowering of plasma, CSF (guinea pig) and brain Aβ levels. A time delay was observed between the plasma exposure profile and the Aβ reduction in brain (Figure 1). The relationship between plasma and brain exposure was linear at the observed time points (not shown). In the population modeling approach the delay in onset of effect in brain was estimated at 26 minutes in mouse and 1 hour in guinea pig (Table 1). In guinea pig brain Aβ40 and Aβ42 have similar turnover rates. The turnover rate of Aβ40 in CSF appears slower.

Correlations

In primary mouse cortical neurons and the N2A mouse cell line our BACE1 inhibitors displayed a concentration dependent inhibition of Aβ release. A 1:1 correlation was observed for the IC50s (not shown). Potency in human SH-SY5Y cells is correlated to potency in mouse and guinea pig primary neurons with a 4.5-fold lower IC50 value in the SY5Y cells (Figure 2).
There is a correlation between the IC50 to inhibit Aβ release in mouse PCN cells (Figure 3) and the N2A cell line (not shown) *in vitro* and effective free brain concentration for a 20% inhibition of Aβ with a 2.5-fold lower IC20% value *in vivo*.

Conclusions

A good correlation between mouse and guinea pig *in vitro* and *in vivo* potency and an excellent correlation between mouse/guinea pig PCN and human SH-SY5Y, increased the confidence in using human cell lines for screening and optimization for effect of novel BACE1 inhibitors. The established *in vitro-in vivo* correlations could thereby reduce the number and change design of preclinical *in vivo* effect studies.

Methods

BACE1 inhibitors were characterized *in vitro* in human SH-SY5Y cells, mouse N2A cells, and in mouse and guinea pig primary cortical neurons (PCN). The PKPD properties of 28 compounds were evaluated *in vivo* using female C57BL/6 mice in single dose, dose- and/or time-response studies (10 compounds). Four compounds were studied in male Dunkin-Hartley guinea pigs. Plasma exposure was converted to free brain exposure using brain exposure, plasma protein and brain binding (Friden et al, 2010). Free plasma or brain concentrations were used as input to inhibition of brain Aβ production rate. For both species, population modeling of all *in vivo* data was performed using NONMEM and an indirect response model with inhibition on the Aβ production rate (Dayneka et al., 1993) to estimate the unbound brain concentration giving 20% inhibition from baseline (IC20%).

Acknowledgements

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References

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Fridén M, Ljungqvist H, Middleton B, Bredberg U, Hammarlund-Udenaes M. Improved measurement of drug exposure in the brain using drug-specific correction for residual blood. J Cereb Blood Flow Metab. 2010 Jan;30(1):150-61.

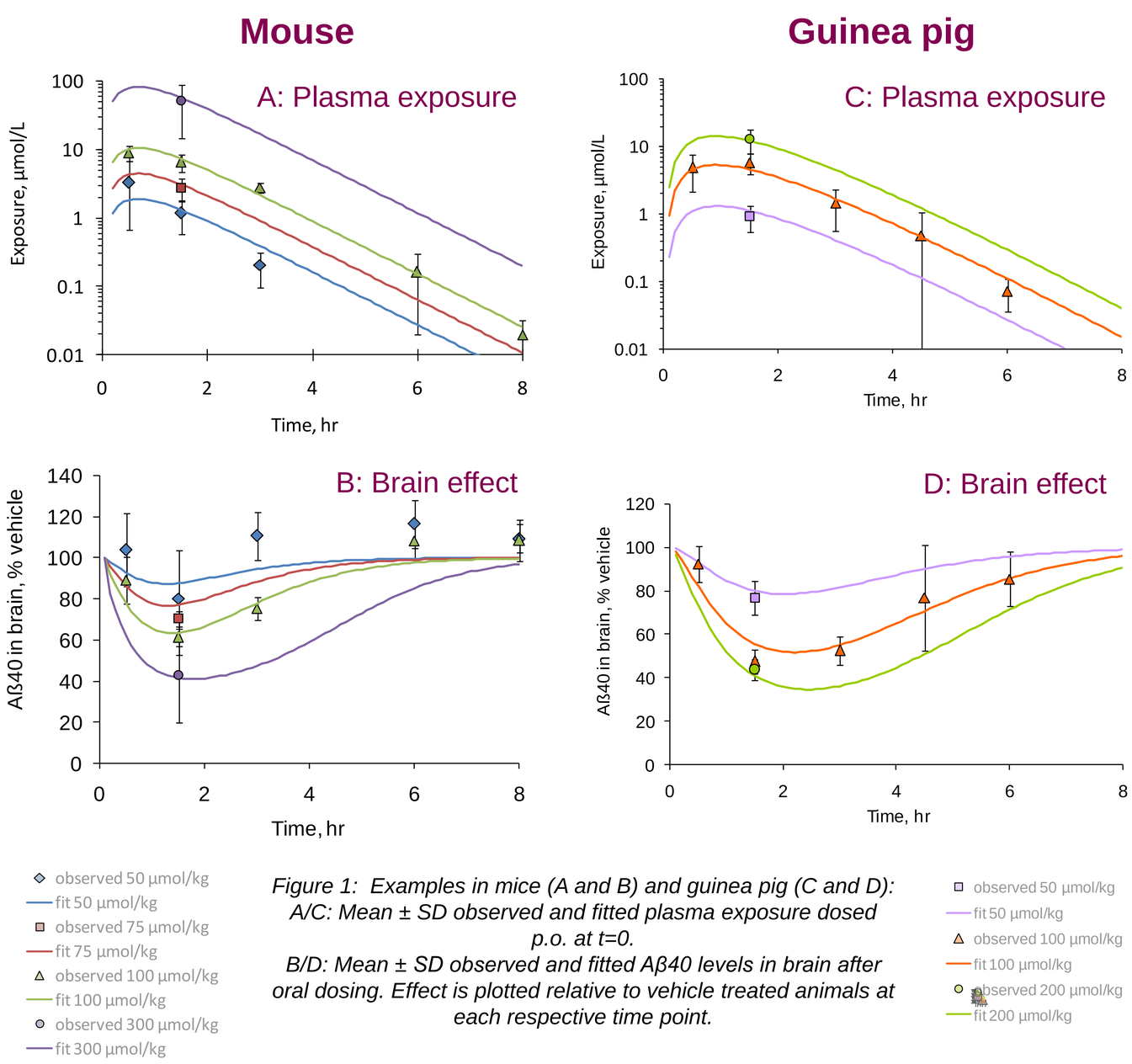

Figure 1: Examples in mice (A and B) and guinea pig (C and D): A/C: Mean ± SD observed and fitted plasma exposure dosed p.o. at t=0.
B/D: Mean ± SD observed and fitted Aβ40 levels in brain after oral dosing. Effect is plotted relative to vehicle treated animals at each respective time point.

Population modeling outcome	Kout (h^{-1})	$T_{1/2}$ Kout (min)	Imax
Mouse			
Aβ 40 in brain vs brain exposure	1.6 (7%)	26	83 (4%)
Guinea pig			
Aβ 40 in brain vs brain exposure	0.7 (4%)	60	100*
Aβ 42 in brain vs brain exposure	0.6 (23%)	69	83 (15%)
Aβ 40 in brain vs plasma exposure	0.6 (9%)	65	100 (7%)
Aβ 40 in CSF vs plasma exposure	0.5 (13%)	92	92 (9%)

Table 1: Key PKPD population modeling outcome (relative error of mean).
** Value indirectly estimated using IMAX=EXP(THETA(x))/(1+EXP(THETA(x)))*

In vitro-in vitro correlation

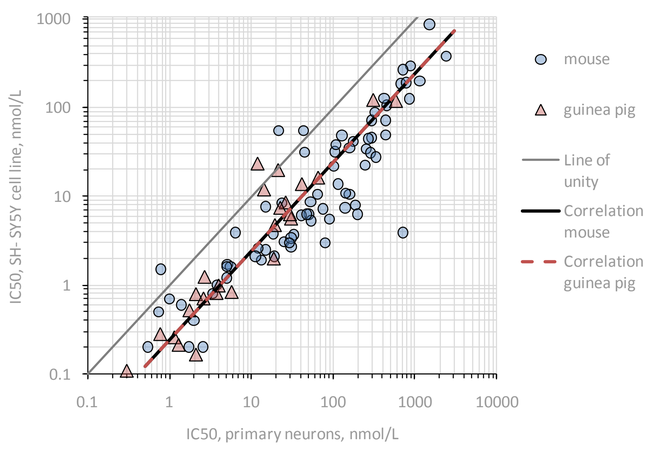

Figure 2: Potency in the human SH-SY5Y cell line vs potency in the mouse and guinea pig primary cortical neurons.

In vitro-in vivo correlation

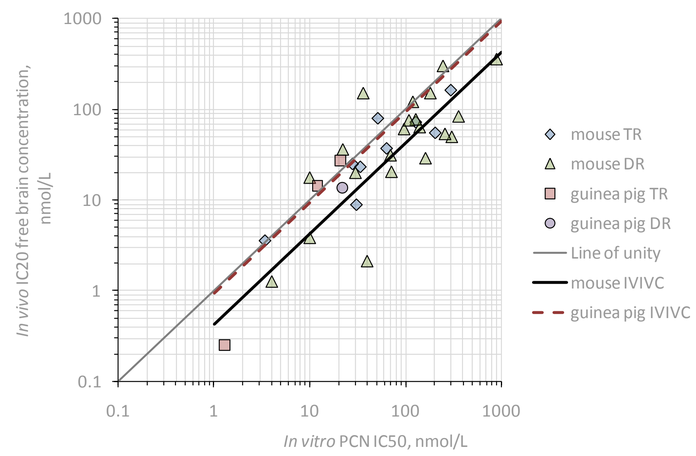

Figure 3: Free brain concentration at which 20% reduction in brain Aβ40 is achieved, estimated in a population analysis using the indirect response model vs IC50, potency in the primary mouse or guinea pig neurons, respectively. TR reflects compounds run in a time-response experiment. DR reflects compounds run in a dose-response design at one time point.

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