

Pharmacokinetic-Pharmacodynamic Analysis of Central & Peripheral Effects of GSK3 β Inhibitors

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Introduction

Alzheimer's Disease (AD) is the most common cause of dementia in the elderly. GSK3, a serine/ threonine kinase, has been implicated in the aberrant hyperphosphorylation of tau leading to Neurofibrillary Tangles, a key neuropathological hallmark of AD.

Objectives

The aim was to perform a pharmacokinetic- pharmacodynamic analysis of central and peripheral effects of five GSK3 inhibitors in rat pups, and to correlate these effects to *in vitro* pharmacology measures. And to investigate the influence of plasma protein binding and distribution to the brain.

Data

Each compound was administered at one to three dose levels and the exposure in plasma and in hippocampus was measured at one time-point in each individual. At the same time-point the phosphorylation of Tau in the hippocampus (central biomarker) was measured at two epitopes (AT8 and AT180). Also, the phosphorylation of glycogen synthase in muscle (P-GS) was measured as a peripheral biomarker (Fig1). *In vitro* pharmacology data, brain binding in adult rat brain and plasma protein binding in rat pup plasma was also available.

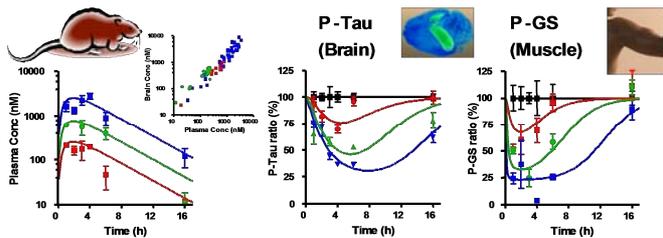


Figure 1: Example of data collected for each compound. It is clear that the time to maximal inhibition is different in brain (mid panel) and in muscle (right panel).

Methods and models

For the model building a mixed effects modelling approach was used since there was only one observation of each biomarker per animal. "Individual data" were created by grouping data per study and per compound evaluated giving 21 study/compound combinations. The variability between different study/drug combinations was also evaluated.

The plasma concentrations were used to drive the response and all compounds were simultaneously fitted in one model. The central effects were best described by indirect response models that could account for the delay in onset of this effect, while the peripheral effect was described by a direct effect model.

Translational Opportunity

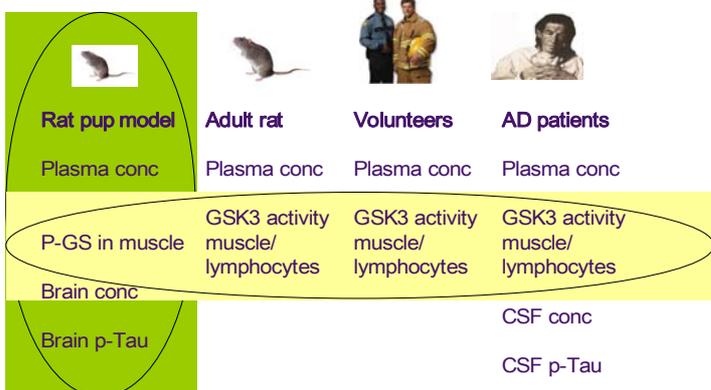


Figure 4: Translational plan for GSK3 inhibitors where the peripheral GSK3 activity could be measured in muscle and/or in lymphocytes.

Results

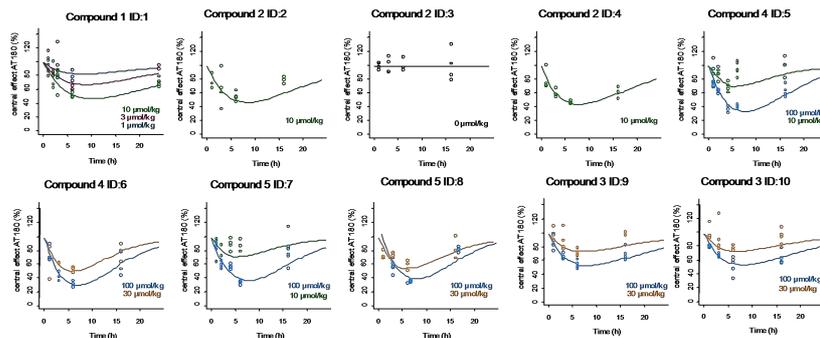


Figure 2: Example of model predictions of the central effect on AT180.

The drug specific parameter IC_{50} could be estimated for all effect measures and the rank order of these values was similar for the three effect measures (Table 1). The average half-life for the delay in the central effect was 2.7 h for AT180 and 4.1 h for AT8.

Table 1: Parameter estimates for the central (AT180 and AT8) and peripheral (P-GS) effects of five GSK3 inhibitors.

Parameter	AT180	AT8	P-GS	
	Parameter estimate (CV%)	Parameter estimate (CV%)	Parameter estimate (CV%)	Parameter estimate (CV%)
IC_{50} , nM			IC_{50} , nM	
Compound 1	113 (13)	85.1 (30)	Compound 1	91.2 (16)
Compound 2	614 (27)	1670 (40)	Compound 2	1980 (5)
Compound 3	13100 (30)	17700 (37)	Compound 3	10400 (9)
Compound 4	313 (27)	229 (31)	Compound 4	379 (11)
Compound 5	962 (19)	521 (31)	Compound 5	576 (9)
Kout, 1/h	0.26 (15)	0.17 (8)	E0, %	102 (1)
Kin/Kout	98 (1)	93.4 (2)	Imax, %	1 fixed
Imax, %	1 fixed	1 fixed	Gamma	1.13 (12)
Gamma	0.83 (19)	1 fixed		
lIV on Kout, %CV	19 (60)			
Res error proportional, %	15 (13)	29 (10)	Res error additive	22 (8)

There was a good correlation between *in vitro* data and *in vivo* parameter estimates (Fig 3, right). Also, the IC_{50} for peripheral and central effects showed a good correlation (Fig 3, left). Correcting for plasma protein binding and distribution to the brain did not change these correlations.

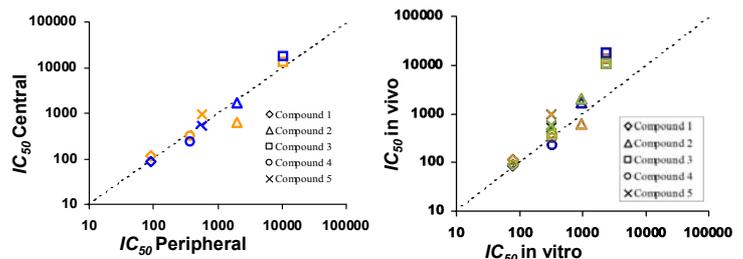


Figure 3: Good correlations between central and peripheral effects (left panel) and between *in vitro* and *in vivo* measures of GSK3 activity (right panel).

Conclusions & perspectives

The response of the GSK3 inhibitor on P-GS seems to well predict the compound potency for its central effect, although not for the time-course of this effect. This provides a translational opportunity for rat to human extrapolation by characterizing P-GS as a peripheral biomarker in both species (Fig 4). Additionally, the good *in vitro-in vivo* correlation can be used to benchmark new candidate drugs, showing inhibition of GSK3 *in vitro*, thereby reducing the need for *in vivo* screening experiments.



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