A Quantitative Systems Pharmacology model of the nerve growth factor (NGF) pathway to aid drug discovery and development

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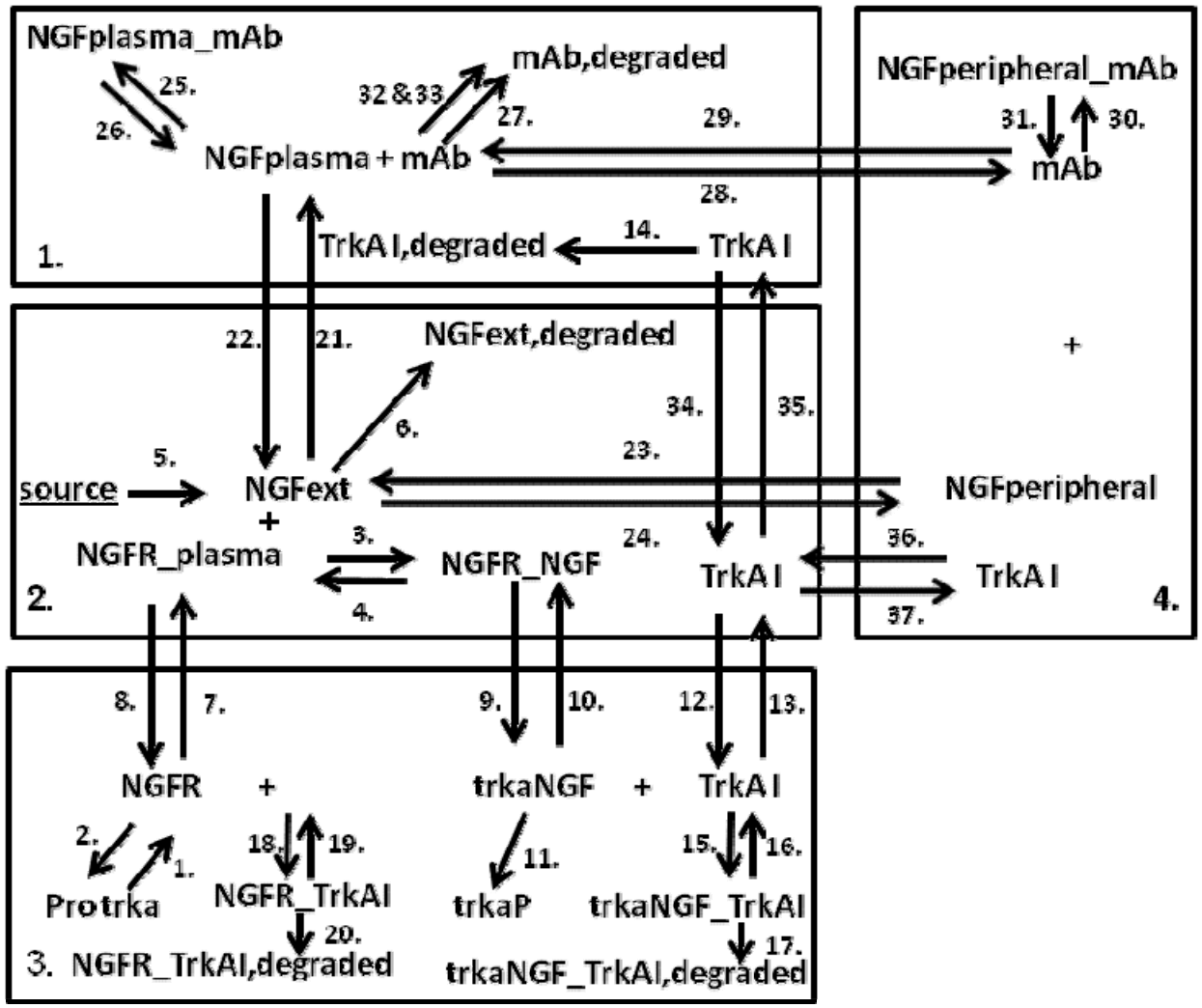
The NGF pathway is of great interest as a potential source of drug targets, for example in the management of certain types of pain. The biology of the NGF response has been studied over a number of years in great detail and the aim of this work was to integrate this knowledge in a Quantitative Systems Pharmacology (QSP) framework to guide drug discovery and development programs, in particular with regards to novel drug target identification, target validation, biomarker and biomeasure [1] selection, dose prediction and ultimately patient selection ("precision medicine").

In sensory neurons, NGF engages with its receptor known as tropomyosin receptor kinase A (TrkA) and following auto-phosphorylation, the NGF:TrkA complex is internalised and trafficked to the neuronal cell bodies. Here it is then thought to cause an accumulation of diphosphorylated extracellular signal regulated kinase (dppERK) in the nucleus and subsequently the expression of numerous genes related to neuronal survival and pain sensation. Arguably the dppERK concentration could therefore be regarded as a biomarker of pain response. Two Systems Biology models for describing the events leading to dppERK migration [2] and nuclear-cytoplasmic shuttling of ERK [3] were coupled resulting in an ordinary differential equation model comprising 59 molecular species and 233 parameters. To facilitate the evaluation of drugs with diverse molecular properties from small molecules to monoclonal antibodies, this 'systems biology' model was converted into a more physiologically realistic integrated QSP model by expressing it in three inter-connected compartments representing the neuronal, interstitial fluid and plasma compartments (Scheme 1) with the signal transduction reactions expressed in the neuronal compartment. The model was calibrated using in-house and external preclinical and clinical data. All analyses were performed using Simbiology 2011b (Matlab, Natick, USA).

Using sensitivity analysis it was concluded that after NGF itself, TrkA was one of the most sensitive druggable targets (**target selection**). With the focus on TrkA, the model was then used to explore the characteristics required for a successful hypothetical TrkA inhibitor (**target validation**) relative to a monoclonal antibody. Thereafter, using in house pharmacokinetic (PK) and equilibrium binding constant data (K_i) data, the model was used to provide **dose predictions** for new entities, as a complement to data from animal models of 'disease'and *in vitro* assays.

We concluded that a hypothetical drug with typical PK and pharmacological characteristics could significantly inhibit the NGF pathway signalling at conceivable plasma concentrations and doses. However, the model also raised the caveat that the TrkA concentration strongly influenced the observed response and potentially the conclusions. Hence, TrkA concentrations were experimentally determined in a range of cell types including a mammalian neuronal cell line. We found that levels varied markedly between cell types, highlighting the need for a reliable estimate in a relevant human cell type. QSP models incorporating such biomeasure data could be of great utility at all stages in drug discovery and development.

Scheme 1.



Scheme 1. (1) refers to compartment 1 the plasma compartment of 3.35L. (2) is the interstitial fluid compartment (12L) (3) is the neuronal intracellular compartment (0.001L) and (4) is a peripheral compartment (2.85 L). I refers to a Mg.ATP non-competitive inhibitor of TrkA kinase and is assumed to be in rapid equilibrium between the compartments.

References:

[1] Van der Graaf P & Benson N (2011) Pharm. Res. 28, 1460-1464
[2] Sasagawa S *et al.* (2005) Nature Cell Biol. 7, 365-372
[3] Fujioka A *et al.* (2006) J. Biol. Chem. 281, 8917-8926