IN SILICO MODELLING FOR *EX VIVO* RELIABILITY

Validation of biological methods via computer simulation

PROBLEM DESCRIPTION

Receptor reserve is an integrative measure of response-inducing ability of the interaction between an agonist and a receptor system (consisting of a receptor and its signaling). The determination of receptor reserve is challenging for agonists with short half-lives, such as adenosine. Although adenosine metabolism can be inhibited several ways (in order to prevent the rapid elimination of adenosine administered to construct concentration-effect (E/c) curves for the determination), the consequent accumulation of endogenous adenosine biases the results. To address this problem, we previously developed a method, by means of which this bias can be mathematically corrected.

CHALLENGES AND GOALS

To validate our new method to assess receptor reserve as a possible tool for drug development

CHALLENGES: Health, demographic change and wellbeing

PRODUCTIVE SECTOR: Biomedicine and Health Care

MATHEMATICAL AND COMPUTATIONAL METHODS

A computer simulation was carried out through *in silico* reconstruction of selected *ex vivo* E/c curves describing the direct negative inotropic response to adenosine and CPA, two A_1 adenosine receptor agonists, in isolated and paced guinea pig left atria. As receptor function model, the operational model of agonism was chosen to link the agonist concentration to the effect. Values for concentrations and parameters of the operational model were received from biological measurements or rendered arbitrarily.

To transform the *in silico* E/c curves, the known mechanisms of action of chemicals used for the original *ex vivo* experiments were translated into algebraic operations, furthermore, where appropriate, the receptorial responsiveness method (RRM) was applied. The aim of simulation was to position the *in silico* E/c curves to overlap the corresponding *ex vivo* E/c curves as perfect as possible, and, as long as possible, in line with our biological knowledge. When an algebraic operation contradicting this biological knowledge had to be introduced to reach the appropriate overlap, this was followed by making a new biological assumption that could underly the given algebraic operation.

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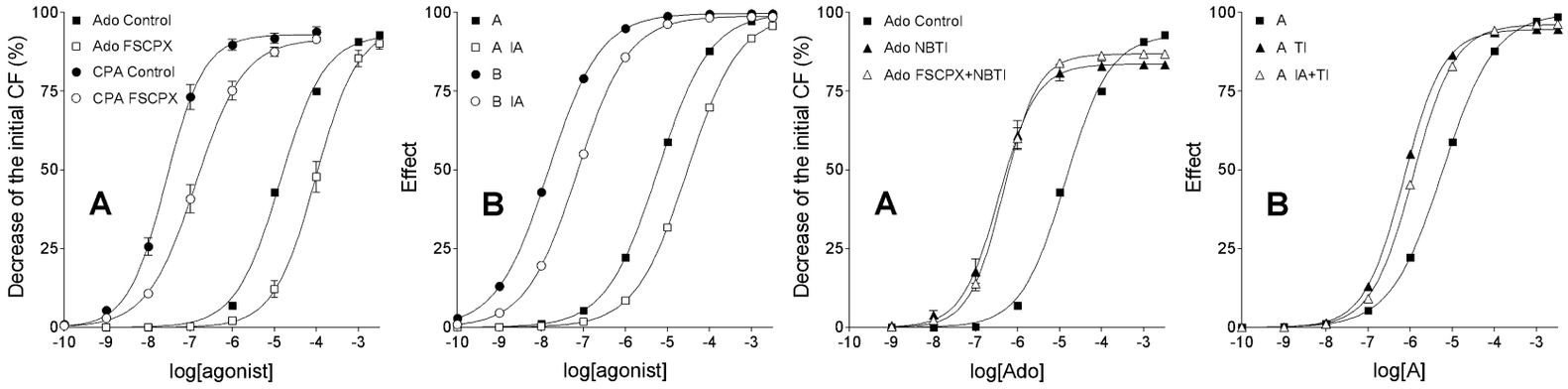
Results and Benefits

Our results provided an *in silico* validation for determining receptor reserve for adenosine, an agonist with short half-life, by means of our recently developed method. In addition, our results suggest that FSCPX and NBTI may interact in a way that FSCPX may blunt the action of NBTI (a finding that, to the best of our knowledge, has no antecedents in the literature). Consequently, our investigation pointed to the importance of *in silico* validation to disclose or exclude unforeseen interactions between treatment schedules (a problem that can occur in every study), and, in general, to shine a light on previous results.

In silico modelling as a tool for method validation and hypothesis formation in pharmacology



A panels: *ex vivo* data to be simulated; **B** panels: *in silico* simulated data; Ado: adenosine; A: simulated adenosine; CPA: a synthetic adenosine analogue; B: simulated CPA; FSCPX: an irreversible adenosine receptor blocker; IA: simulated FSCPX; NBTI: an adenosine transport blocker; TI: simulated NBTI; CF: cardiac (atrial) contractile force

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