IN SILICO MODELLING FOR *IN VIVO* SUCCESS

Hypothesis-driven investigation of a new molecular target for FSCPX, a known molecule

CHALLENGES: Health, demographic change and wellbeing

PRODUCTIVE SECTOR: Biomedicine and Health Care

PROBLEM DESCRIPTION

An emerging possibility in drug development is to find out new molecular targets (and thereby new effects) for well-known drugs. FSCPX (an irreversible A_1 adenosine receptor antagonist) and NBTI (a nucleoside transport inhibitor) exhibit an unexpected (apparently paradoxical) effect pattern when added together to an *ex vivo* guinea pig heart (specifically: left atrium) model. In the presence of NBTI, FSCPX behaves as an A_1 adenosine receptor enhancer.

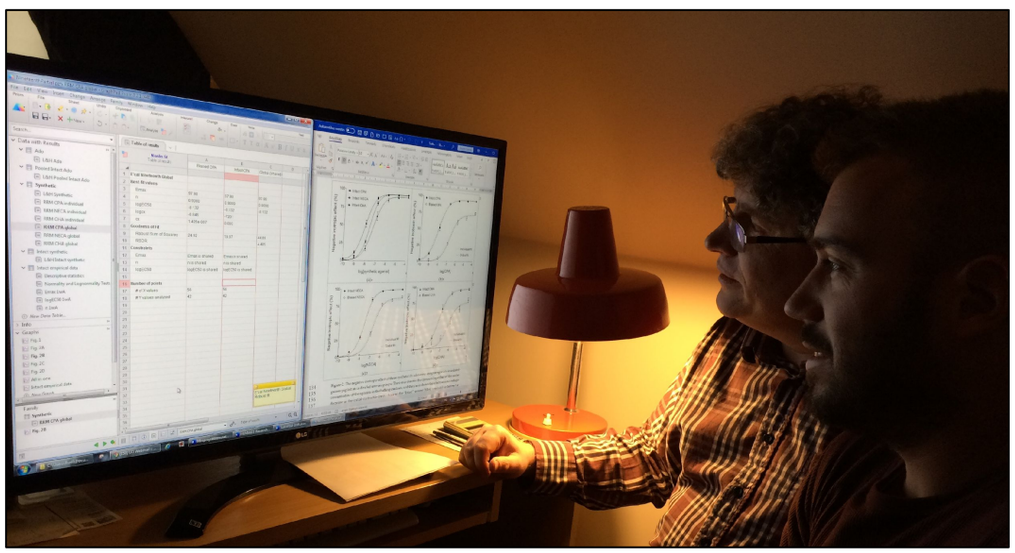
CHALLENGES AND GOALS

To understand the interaction between FSCPX and NBTI

To explore possible new drug targets and mechanisms of action

MATHEMATICAL AND COMPUTATIONAL METHODS

The most exact way to describe the effect of a drug on a biological system is to construct and properly evaluate concentration-effect curves. Under certain circumstances, RRM (receptorial responsiveness method), a procedure created previously by our work team, may serve as a useful tool in the interpretation of concentration-effect curves. During a computer simulation study, properties of FSCPX and NBTI, known and hypothesized ones, were translated into mathematical operations on the parameters of known equations defining the function of the pharmacological receptors (the Hill equation, equations of the operational model of agonism, and the equation of RRM). This way, results of *ex vivo* experiments were simulated and then re-interpreted.



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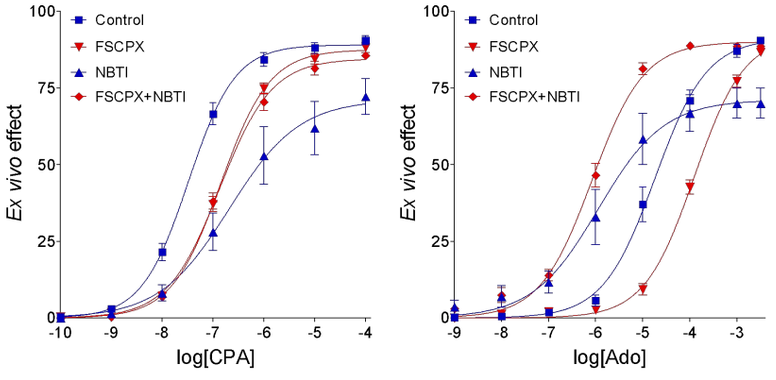
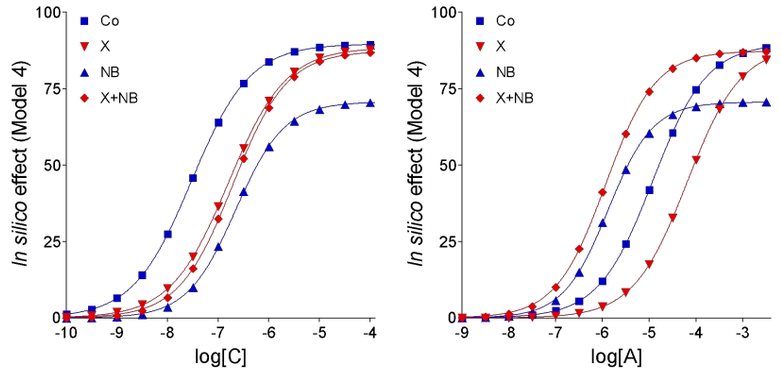
Results and Benefits

Results of our investigation provided in silico evidence for an inhibitory action of FSCPX on the interstitial adenosine accumulation produced by NBTI, a nucleoside transport inhibitor. Regarding the mechanism of this interference, in silico evidence has been obtained supporting that FSCPX only inhibits the interstitial accumulation of endogenous (but not exogenous) adenosine. A possible mechanism of this is that FSCPX inhibits an enzyme participating in the interstitial adenosine formation. This finding may initiate the development of agents that inhibit the interstitial adenosine production and thereby influence the widespread adenosinergic mechanisms throughout the body.

A new mechanism of action identified and a new molecular target hypothesized for a known chemical



Results of ex vivo experiments to be simulated



The simulated concentration-effect curves

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