De- and Resensitisation of Cardiac β-Adrenergic Receptor Signaling: A Modelling Approach

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In the adult heart, two types of β-adrenergic receptors ($β_1$-AR and $β_2$-AR) controls the speed and force of contraction. These receptors are sensitive to isoprenaline (ISO) and cathecolamines. Gs and Gi-proteins associated with the receptor triggers adenylyl cyclase (AC) to produce cAMP. cAMP indirectly elicits contraction of the cells, but it also activates the kinases GRK and PKA which phosphorylate the receptor and regulate breakdown of cAMP in a negative feedback loop.

Once activated the signaling pathway is rapidly desensitised, a behavior which creates a "peak effect" when cAMP or force of contraction of the tissue is measured. The duration of the desensitisation can be measured through a second stimulation of the cells.

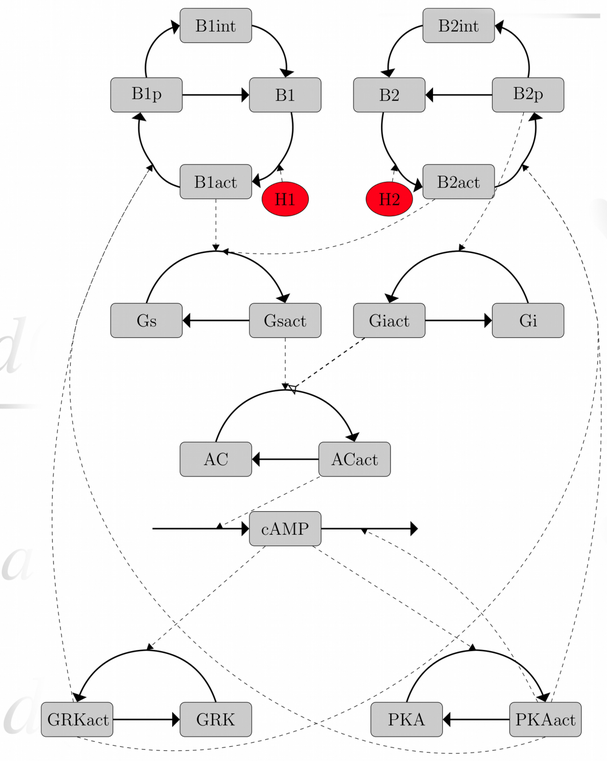


Fig. 1 Original model of the β-AR signaling pathway.

Models

-Mechanistic model using ODE:s describe the signaling pathway to the level of cAMP.

- Original and minimal versions.

- Fitted to theoretical data, tested for return of signal and ability to describe experimental data.

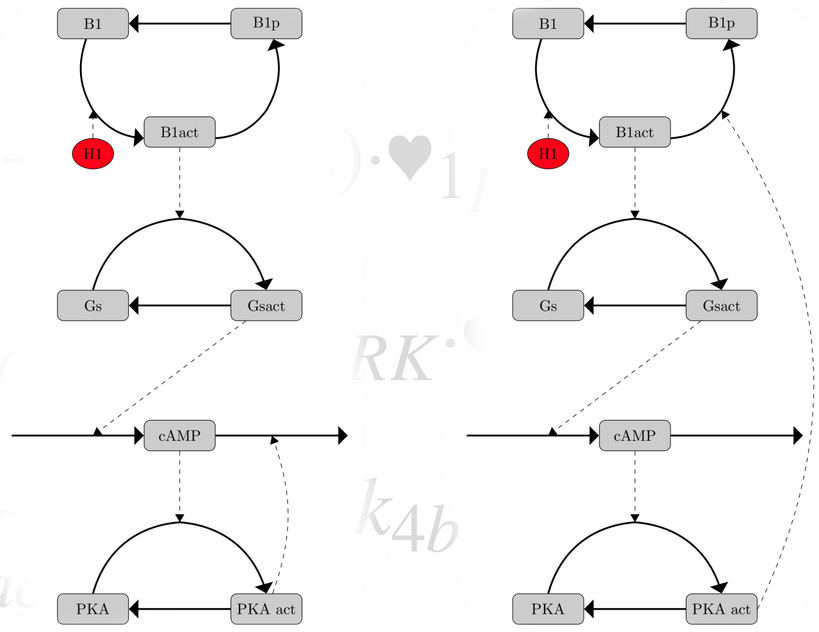
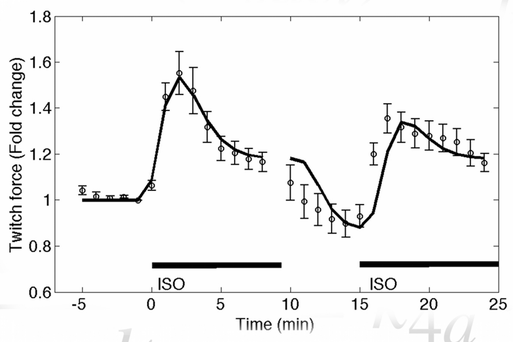


Fig. 2 Minimal models of the β-AR signaling pathway.

Results

Model \ Test	Theoretical data	Return of signal	Experimental data	Predict resting time
Original model	☹	☹	☹	☹
Minimal models	☹	☹	☹	—
All simpler models	☹	—	—	—

A.



B.

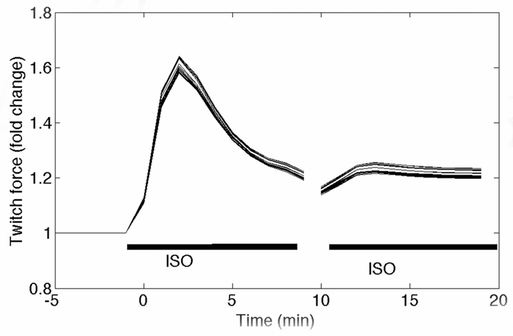


Fig. 5A. Chicken cardiac tissue stimulated twice with ISO. Force of contraction was used as an approximation of cAMP.

B. Model prediction of the strength of the desensitisation after 1 min of rest between the stimulations.

At least three receptor states and one negative feedback loop is necessary to explain the desensitisation!

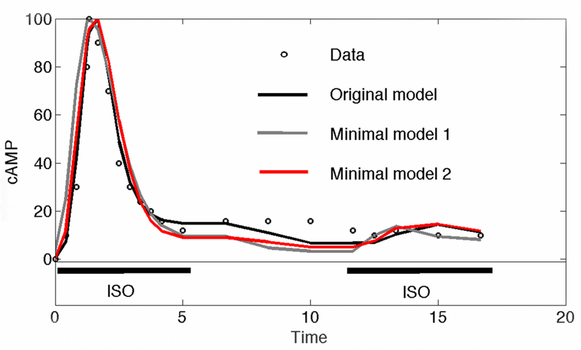


Fig. 3 Simulations of theoretical desensitisation data using the parameter set with the lowest cost found for each model.

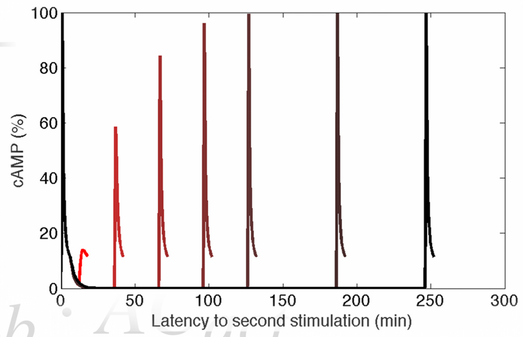


Fig. 4 All three models can simulate the return of the signal in the theoretical data after a longer period of rest between two stimulations.

Future prospects

- Tie GRK phosphorylation closer to internalization.

- Minimal model capable of describing the experimental data.

- Add compartmentation.

- In the fetal heart the β-AR signaling pathway does not desensitize. Using the model to compare the fetal and adult pathways could give a deeper understanding of how they differ.
This in turn might be beneficial in the search for better pharmacological therapies in heart failure.

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