

# FOCUS ON RESEARCH

## STRUCTURE-BASED DRUG DESIGN OF NITROSYLATING ANTI-INFLAMMATORY COMPOUNDS TARGETING THE GLUCOCORTICOID RECEPTOR

### Researchers

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### Aim

The treatment with steroid derivatives is one of the most effective therapies for inflammatory diseases, but therapy is often hampered by side effects. Anti-inflammatory drugs targeting a central steroid-dependent protein ('receptor') have been successfully used for treatment of asthma, allergic rhinitis, rheumatoid arthritis, leukaemia, as well as heart conditions. Recently, a new kind of steroid drug modifying the receptor has been found to exert increased activity and milder side effects. Proper understanding of the molecular effects of this new class of drug at the cellular level will form the basis for drug leads in order to develop improved therapeutic treatment of inflammatory diseases.

### Project Outline/Methodology

In order to understand the effects of these new drugs on the receptor at the molecular level, we set out to study how the receptor is being modified by the drug. Binding of the drug to, and modification of, the receptor was investigated by molecular modelling using various software programmes. At the same time, we attempted to produce the receptor protein for three-dimensional structure determination and experimental characterisation.

### Key Results

The binding of a representative member of the new class of drugs to the receptor was modelled and visualised as three-dimensional structure. The model shows that the drug can bind in two different ways. Our studies therefore predict that the receptor can be modified at two different locations, depending on the way of binding. However, one of the two alternatives is in better agreement with results from earlier studies as to the function of the receptor. We therefore favour this latter alternative which identifies a point of modification that is of high importance for the cellular activities of the receptor and thus an excellent target.

### Conclusions

Based on these results, it is possible to deduce the molecular requirements to make the new drugs fit even better to the receptor. The three-dimensional models will allow accurate measurements to be taken as to shape and length of the drug that would yield the 'perfect fit'. Furthermore, one can infer that the drug-dependent modification of the receptor affects its communication with other cellular components and channels the receptor into a different track that is generally believed to result in lesser side effects.

### What does this study add to the field?

From our data, we can predict that compounds which have functional groups capable of modifying the receptor at a certain location would be good lead compounds for development of glucocorticoid therapy with lesser side effects.

### Implications for Practice or Policy

Development of more effective drugs to combat inflammatory diseases is a costly process and requires a long time. Computer-based modelling can help us to understand what the important groups of promising lead molecules are and hence help us to design better compounds and cut the time that it takes to get new drugs to the market.

### Where to next?

The modelling results have to be confirmed by laboratory experiments. The project is being continued in our group by trying to obtain large enough quantities of the receptor for structural studies.

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