

- Research Project Seeks Funding -

Project Description:

Modelling the Human Steroidal Hormone Cascade

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Summary:

This is a biomedical research project involving laboratory experiments and computer modelling. The objective is to test hypotheses related to the human steroidal hormone cascade. The benefit of this is that if our hypotheses are confirmed, it will be possible to develop **new, effective drugs against cancer, infectious diseases and severe mental diseases**. Research is to be conducted as a cooperation between an Austrian and an Indian group. **For this project, we need funding.**

Objective:

The objective of this project is to discover the chemical reaction kinetics constants for enzymatic reactions taking place in the (human) steroidal hormone cascade and to subsequently develop a computer model that simulates these reactions and allows for a quantitative evaluation of the reaction kinetics.

In particular, we would like to test the hypothesis whether isoflavones, which are supposed to increase the “adiols” (androstenediol and androstanediol), have the desired effect to reduce the concentration of hormones associated with stress reactions and increase the concentrations of hormones associated with immunity.

Previous work:

Previous work has been conducted by the Austrian group, culminating in a publication about the effects of stress on the steroidal hormone cascade in severe mental diseases on the one hand and physical training (for a marathon run) on the other.

This publication is called “**Model Approach for Stress Induced Steroidal Hormone Cascade Changes in Severe Mental Diseases**” and was published in the journal “Hormone Molecular Biology and Clinical Investigation” in January 2016 (Authors: Claus Volko, Pedro-Antonio Regidor, Uwe Rohr).

What each side has to do:

The Indian side is supposed to develop novel biosensors and discover the chemical reaction kinetics constants using these sensors. The Austrian side will then develop and evaluate the computer model.

The Austrian team leader, Claus Volko, has a dual training in both human medicine (MD) and computer science (MSc), as well as more than three years of experience in developing computational physics software, which makes him one of the best qualified persons in the world for conducting this kind of research besides to his expert knowledge on the scientific theory developed by his late friend and mentor Uwe Rohr, who was a pharmacist and medical doctor by training.

Theoretical Background:

Enzymatic reactions are chemical reactions which occur in an organism and make use of a catalyzer (the enzyme). The catalyzer lowers the energy which has to be used in order to make the reaction possible, i. e. it “catalyzes” the reaction. Due to the particular circumstances that work in an organism, such as the body temperature, enzymes are necessary to make (bio)chemical reactions possible.

The enzyme first creates an enzyme-substrate complex together with one of the two chemical compounds that react together. Then this enzyme-substrate complex attaches the other chemical to it and finally the enzyme dissociates, leaving the desired product.

Every chemical reaction may occur in both directions. Usually, in an organism a steady state is ultimately reached, in which one of the two sides prevails. The ratio of the concentrations of the two sides is called the kinetic constant K . It is specific for the reaction.

In order to be able to create a quantitative computer model for enzymatic reactions, it is therefore necessary to know the reaction kinetics constants K for each and every reaction that may occur. This is necessary in order to compute how many chemicals from one side are converted into chemicals from the other side per unit of time.

The steroidal hormone cascade is not a single enzymatic reaction, but a cascade of enzymatic reactions. It may be pictured as a net of roads on a roadmap. Each reaction can occur in both directions, and there are also sideways and short cuts to certain “locations” (i. e. molecules). A computer model of the steroidal hormone cascade is, thus, highly complex. Nevertheless it is possible to create such a model using a common programming language such as C++ or C# without requiring expensive hardware – a common PC as it is available on the consumer market suffices. **All that is important is to have the necessary reaction kinetics data and to know which reactions occur in the cascade.**

As a matter of fact, the Austrian team leader has already developed a prototype of a program that could simulate such a computer model and make all the relevant calculations. This prototype would only have to be fed with data, and tested.

The Austrian team leader has previously worked with the late Uwe Rohr, his friend and mentor, who investigated the effect of soy isoflavones on various types of cancer and severe mental diseases, as well as wound healing. Uwe Rohr observed that high doses of soy isoflavones had a positive effect on all of these conditions. He then formulated the hypothesis that this effect may be caused by modifications of the steroidal hormone cascade induced by soy isoflavones.

There are several publications from Uwe Rohr and colleagues which deal with the effect of soy isoflavones and try to explain it. In particular, we recommend reading the publication “Model Approach for Stress Induced Steroidal Hormone Cascade Changes in Severe Mental Diseases”, of which the Austrian team leader Claus Volko was the first author. This publication is based on an exhaustive literature survey, and among others, the alterations of testosterone, estradiol, androstenediol, androstenediol, dehydroepiandrosterone, cortisol, aldosterone, and progesterone were observed and evaluated.

Uwe Rohr proposed that the effect of soy isoflavones, which are also to be found in other natural products, e.g. red clover, is due to alterations of the concentrations of the so-called adiol, i. e. androstenediol and androstanediol. According to Uwe Rohr, not all steroidal hormones have an immunosuppressive effect, as it was previously believed. Rather than that, he suggested that some steroidal hormones are used to make the body adapt to stressors, which has the effect that the immune system is temporarily shut down, while other steroidal hormones actually have positive effects on the immune system. **Uwe Rohr was convinced that the adiol is among those steroidal hormones which have a positive effect on the immune system, and he suspected that by increasing the concentrations of the adiol, the concentrations of stress-related steroidal hormones would shrink, which would have an overall beneficiary effect on physical as well as mental health.**

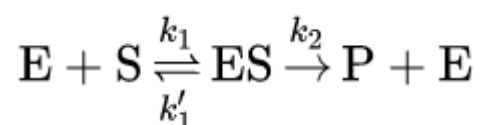
Also, Uwe Rohr came to the conclusion that the late Carl Djerassi had made a grave mistake by synthesizing cortisone, which is an inflammatory drug that shuts down the immune system, while the adiol is not only inflammatory but also boost the functionality of the immune system. This view is still a bit controversial since many established physicians fail to accept that an anti-inflammatory effect can be created without shutting down the immune system.

As a consequence, Uwe Rohr and Claus Volko have made an effort to conduct research trying to find evidence that supports Uwe Rohr's hypotheses, and they have already been partially successful.

The development of an accurate computer model of the human steroidal hormone cascade would enable researchers to additionally test Uwe Rohr's hypothesis regarding the conversion of stress hormones into immunity hormones by increasing the concentration of the "adiol" and therefore lay a solid scientific basis for the development of new, effective drugs against cancer, infectious diseases and severe mental diseases, and to support wound healing.

Mathematical Methodology:

Enzymatic reactions follow the Michaelis Menten kinetics, which looks as follows:



k_1 , k_1' and k_2 are chemical reaction kinetic constants. It is the task of the Indian side to obtain these values experimentally. The computer model developed by the Austrian side will use the obtained values in order to calculate the concentration of the product resulting from the reaction of the enzyme with the substrate.

The value k_1 specifies how many molecules of the substrate are converted into the enzyme-substrate complex per unit of time. Likewise, the value k_2 specifies how many molecules of the enzyme-substrate complex are converted into the product per unit of time. In other words, using time-discrete modelling, the program can assume that in each time step, a particular number of molecules from the substrate is converted into a particular number of molecules of the product, signified by the constants k_1 and k_2 . The program will then use network modelling in order to compute the concentrations of all the hormones involved in the cascade, i. e. it will start with one substrate, compute the concentrations of the substrate and the product after the time step, then take the product as the new substrate and do the same computations, etc.

Novelty of the Project:

The chemical reaction constants of the enzymatic reactions involved in the human steroidal hormone cascade were supposedly investigated by German researchers in the 1930s, but a literature survey yielded insufficient results. It can therefore be assumed that their research work was only of partial nature and that not all chemical reaction constants relevant for this project have been experimentally obtained yet. By conducting these chemical experiments we will thus not only lay the foundation for the mathematical modelling and the computer simulation to verify the hypotheses of Uwe Rohr, but also for further research dealing with steroidal hormone cascades.

No mathematical model of the human steroidal hormone cascade has ever been made before, which is due to the missing data about the chemical reaction kinetics constants. **Thus, all of our work will be entirely novel, pioneering work.**

Selected Publications of the Austrian side (follow the links to obtain the full papers):

[C. Volko, P. Regidor, U. Rohr: Model Approach for Stress Induced Steroidal Hormone Cascade Changes in Severe Mental Diseases. In: Hormone Molecular Biology and Clinical Investigation, January 2016.](#)

[P. Regidor, C. Volko, A. Schindler, U. Rohr: The evolution of genomic stability to a mechanism in reproduction and psychiatry. In: Hormone Molecular Biology and Clinical Investigation, June 2016.](#)

[C. Volko, U. Rohr: Can Plants' Ability for DNA Repair and Stress Defense be Used against Patients' Circulating Tumor Cells? In: Journal of Pharmacy and Nutrition Sciences, October 2015.](#)

U. Rohr, C. Volko, A. Schindler: Comparison of steady state development and reduction of menopausal symptoms after oral or transdermal delivery of 17- β -estradiol in young healthy symptomatic menopausal women. In: Hormone Molecular Biology and Clinical Investigation, February 2014.

M. Samwald, V. Stefanov, G. Petz, C. Volko, A. Hanbury: Improving the quality and findability of open medical information on the web: Medical Wikidata and the FindMeEvidence search engine. In: Proceedings of Medicine 2.0, October 2014.

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