V. „SYSTEMS PATHOLOGY“

- MOLECULAR CONNECTIONS WITHIN AND BETWEEN ORGANS -
- **Stress paradigm** is still of importance, nowadays better understanding of the molecular interaction between CNS, endocrine system and immune system

- Understanding dynamics of differently behaving subsystems is important

- Understanding signalling links in co-morbidity

- Computer-based modelling and simulation is important to have a realistic understanding of the differential superimposing relevant processes (e.g. eating, insulin, glucagon...)
STRESS-PATHOLOGY: UNIVERSAL RELEVANCE WITH THE BRAIN AS FOCUS

Control loops
- What are the regulative principles?

**PSYCHOLOGY**
Stressor, „anxious stimulus“ is perceived, already „prerefexive“ processing evokes somatic reaction

**PHYSIOLOGY**
amygdala etc. are signalling downstream, evoking noradrenergic responses and an adaptive down-regulation of the stress-response system, „Allostasis“

**PATHOLOGY**
- Depression..Diabetes...

Grafic S: Touma
V. 1 DIABETES MELLITUS

THE CELL AS A NETWORK OF MOLECULAR NETWORKS
- DIABETES AND BETA-CELLS OF PANCREAS -

„GENOMICS, TRANSCRIPTOMICS, PROTEOMICS, METABOLOMICS…“
DIABETES MELLITUS

- **Symptoms:** polyuria, sugar in urine, polydipsia, blood sugar elevated, slow remission under glucose stress,

- **Diagnostics:** BG, UG ....

- **Nosology:** Type I, Type II, several other types can be differentiated (common problem in medicine!)

- **Complications:** microangiopathy in all organs,
DIABETES MELLITUS

- **Pathophysiology:** insufficient insulin system (different etiologies); genes? , immune system? nervous system? ....conditions, interactions, production deficiency, reception deficiency, regulation deficiency ???
  Nutrition, ..Stress ...?

- **Therapy:** anti-diabetic drugs, insulin, dietary regulations, ....

Challenges (from molecule to organism...):

- Multi-focal intervention, undermining the differential dynamics of components
Blood sugar as target variable..., controlled by insulin... but also other agents!!!

And: Relative Antagonism

Abbildung 3.4: Die Regulation der Blutglucosekonzentration. Rot: erhöht die Konzentration.
- coincidence of depression and diabetes
- cortisol as common component with elevating effect on blood sugar as target variable.
- HPA axis: dysregulated in depression and under stress
- HPA axis: influence on blood sugar / insulin
- Chronic stress can modulate manifestation of d.m.
CIRCULAR CASCADES:
psychosocial stress -> (nor)adrenaline + cortisol oscillations measured & simulated
(s. Fig. below; from Tretter et al. 2011)

Similar fluctuations: ->...:blood glucose -> insulin –I blood glucose -> hunger, eating -> blood glucose -> insulin ...
(-> = ACTIVATES...;-I = INHIBITS, REDUCES...).
DYNAMICS
FLUCTUATIONS, OSCILLATIONS AND REACTION TYPES

Spontaneous fluctuations of insulin release

also circadian / infradian:
Parathormone, Cortisol, …
Noradrenaline,
Acetylcholine, ….

Opposing asymmetric reactions to food intake: Gluc, Ins, Glug..

Eating =>
Glucose +,
Insulin + +,
Glucagon -,
Glucose - =>
Glucagon +…
Time has now come to test the Hovorka model, to see if the results are sensible. We will begin with testing a single day in some different scenarios, and hopefully get some more insight in what it means to be a diabetic, which can finally lead to a better GUI.

3.2.1 Insulin before or after meal

First of all it would be interesting to see at what time it's best to take your insulin relative to the time of your meal, in order to stay in the good interval. We will test this by taking the exact same scenario in two cases, with exception of the time for insulin injection. In this case, we would first of all like to know if it's best to inject before or after a meal. So here we choose to test meal, i.e. -30min and meal, i.e. +30min for i = 1, 2, 3 which represent breakfast, lunch and dinner in a normal day. Just as a point of reference we use CHO1 = 45g and CHO2 = CHO3 = 70g, which means that we assume that the amount of carbohydrates eaten for breakfast is 45g, and so on. The insulin doses are also exactly the same with 2U/L for breakfast and 3U/L for lunch and dinner. Finally we here assume that the duration of a meal is 30 minutes.

As it's obvious to see, there is a tremendous difference in the two graphs. The blue graph represents the 'before case' and the black the 'after case'. The before case is smooth and inside the green box at all times. From this, it is also clear to see that it's a lot harder to control the blood sugar properly when you are Insulin taken before (blue) and after (black) meal.

S: Man-Rizza-Cobelli modell; comp. Lassen & Nielsen 2007
COMPUTATIONAL MODELL OF DIABETES BASED ON SYSTEMS DYNAMICS METHODOLOGY

causal loops are defined by data and expert–based guesses, then a computer simulation is tested and new data are gathered etc.

http://www.systemdynamics.org/conferences/2013/proceed/papers/P1411.pdf

SUMMARY V - SYSTEMS PATHOLOGY

- „reload“ cybernetical physiology, especially stress biology!
- Test concepts / procedure at special disease
- Identify problems that can be solved by systemic approach on different / organismic levels
- Proceed to process model of organism’s health and disease, connecting physiological and chemical levels