



IRON REGULATION IN THE INTACT ORGANISM – KINETIC DESCRIPTION OF THE PATHWAY NETWORK⁺

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Ionic iron is the catalytic component of vital oxido-reductive and oxygen transporting processes in every living cell. In case of excess supply and dysregulation iron becomes a potent cell poison. The mammalian organism maintains a complex regulatory network of iron uptake, excretion and intra-body distribution in which intracellular regulation in different cell types is intertwined with a global hormonal signalling structure.

Based on numerous experimental data obtained over the last half-century we undertook a quantitative description of this subsystem of interacting pathways. Flux rates between organs measured with radioactive tracer in the intact animal, biochemical content in various fractions of bound iron in different cell types, kinetic measurements of iron regulation in isolated cells and molecular studies of iron-related signalling cascades resulting in transcriptional and translational physiological adaptation have supplied the input of quantitative data into the flux-rate and pool model. Black-box description of regulatory pathways (the fine-tuned molecular interactions of which are not amenable to detailed numerical description) was integrated on the global level. Dimensionless variables relative to an idealized “normal” steady-state of the organism were introduced, and the kinetics of single reactions was reduced to linear or power-law description in the neighbourhood of this reference state.

The integrated model was parametrized to simulate the special case of healthy mouse raised under different iron-dietary regimes, under physiological stress (blood loss, iron depletion) and pathological deviation (mutation in crucial iron-related genes). Knock-out and enforced over- or underexpression of genes targeted to different murine tissues and cell types are under way in many experimental groups, and the iron status in these perturbed states will serve as base of a more detailed mathematical analysis of the inter-inter-cellular network interaction of this complex metabolic system.