ISMRM Workshop

MR Imaging of ^{n}X-Nuclei (^{23}Na & Friends):
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Session 6: Sodium MRI Measurements

Can Intracellular Sodium Concentration be Measured?

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SUMMARY

Ion homeostasis

- Ion homeostasis is the steady-state maintenance of highly asymmetric concentrations of the major inorganic ions (Na^+, K^+, Ca^{2+}, Cl^-) between intracellular and extracellular spaces of mammalian cells.
- The regulation of these ionic gradients is critical for cellular functions such as maintenance of intra- and extracellular pH and of cell viability, and propagation of the action potential in neurons for example.
- Well-defined transmembrane ionic gradients are necessary to absorb vital substrates (e.g. glucose), to release products (e.g. neurotransmitters), regulate intracellular metabolite concentrations (e.g. ions), allow energy production (e.g. oxidative phosphorylation), eliminate toxic byproducts (e.g. amyloid oligomers), and control cell volume by regulation of the osmotic pressure responsible for the water flux in and out the cells.
- Maintenance of these ionic gradients is an energy-consuming process that is strongly linked to cell metabolism.
- Gradient of sodium concentrations is maintained transmembrane ions transporters, mainly by Na^+/K^+-ATPase (sodium-potassium pump)
- Normal conditions: intracellular sodium concentration ISC = 10-30 mM, extracellular sodium concentration ESC = 135-145 mM.
- Intracellular Na^+ concentrations are very sensitive to changes in the metabolic state of cells and to the integrity of their membranes.
- Cells in healthy tissues can maintain this large Na^+ concentration gradient between the intra- and extracellular compartments, but any impairment of the energy metabolism or

damage of the cell membrane integrity will lead to an increase of the intracellular Na^+ concentration, and concomitant variations of intracellular and extracellular volume fractions.

- The Na^+ flux in and out of the cells can occur through several mechanisms: passive transport by ionic-specific channels (flux along the gradient), or active transport through different types of exchangers, co- and anti-transporters (flux against the gradient).
- Examples of these transporters include Na^+ channels, Na^+/Ca^+ exchangers, Na^+/H^+ exchangers, $Na^+/K^+/2Cl^-$ cotransporters, and, most importantly, the Na^+/K^+-ATPase.
- These ionic transporters can be impaired (malfunction, destruction, blockage) or dysregulated (lack of ATP) in pathologies, which will lead to variations (mostly increase) of ICS.
- Measuring ISC in vivo with MRI could provide new metabolic information on pathologies (diagnosis, prognosis) or help monitor therapies (cancer).
- Examples of pathologies that could benefit from ISC quantification in vivo: brain tumors, breast cancer, stroke, cardiovascular diseases (myocardial infarction), musculoskeletal diseases (osteoarthritis, Duchenne muscular dystrophy, channelopathies), neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, multiple sclerosis, traumatic brain injury), kidney impairment, diabetes, hypertension, …

MR methods proposed to measure ISC

- Shift reagents
    - $Tm(DOTP)^{5-}$
    - $Dy(TTHA)^{3-}$
    - $Dy(PPPi)_2^{7-}$
- Diffusion
- Relaxation:
    - Inversion recovery (T1)
    - Multiple quantum filters (biexponential T2):
        - Double quantum filter (DQF)
        - Triple quantum filter (TQF)
    - Optimal control theory (T1, T2)
    - Multipulse simulation (T1, T2)
- Other:
    - Direct detection of multiple quantum coherences (MQC)?
    - Quadrupolar filter by nutation?
    - Frequency sweep?
    - More…?

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