Course: Diabetes Hybrid Imaging

MR Imaging & Spectroscopy of the Influence of Insulin Resistance

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Highlights:

- Magnetic resonance imaging (MRI) and spectroscopy (MRS) can be used in various organs to evaluate the effect of insulin resistance (IR). While the major target of this course is the musculoskeletal system, the use of MRI/MRS in studies of IR in the liver, heart, pancreas, and for the determination of whole body composition are briefly addressed.
- Skeletal muscle contains two types of lipids that can be distinguished by ^{1}H-MRS: intra- (IMCL) and extramyocellular (EMCL) lipids. IMCL are metabolically active molecules in small droplets close to the mitochondria which are related to IR, however, not as a cause but rather as a consequence of an unbalanced lipid metabolism.
- IR affects glucose uptake and thus the replenishment of muscular glycogen which can be followed by ^{13}C-MRS. Intermediate products like glucose-6-phosphate can be observed by ^{31}P-MRS.
- ^{31}P-MRS saturation transfer experiments can determine flux through biochemical reactions and results have been interpreted as mitochondrial activity in IR; however, since glycolysis also contributes to the measured flux, the specificity of this method for mitochondrial activity is disputed.
- Recovery of ^{31}P-phosphocreatine is related to oxidative phosphorylation and thus mitochondrial activity. Also specific for mitochondrial activity is the determination of the flux through the TCA-cycle by the observation of infused ^{13}C-labeled substances.
- Hyperpolarized ^{13}C substances are recently used to evaluate the effect of IR on metabolism, currently in particular in liver and heart.

Various reviews provide an extended list of citations dealing with the effect of IR and its observation by MRI/MRS [1-18].

Insulin resistance (IR), the (more epidemiologically motivated) “metabolic syndrome”, and overt diabetes are an interrelated complex of diseases which are affecting lipid- and carbohydrate metabolism. They represent major risk factors for cardiovascular diseases with serious consequences for the patients such as heart failure and cerebral stroke. Meanwhile, the number of affected subjects reaches endemic dimensions resulting also in an enormous threat to our health care systems. Several underlying mechanisms are currently discussed: (a) lipotoxicity, (b), mitochondrial activity (c) inflammation, and (d) oxidative stress [19-26].

MRI/MRS can determine the effect of IR on the metabolism and body composition in various organs. This is particular helpful in organs where biopsies are difficult such as in the liver or in the heart [27-40]. While ^{1}H-MRS is accepted as the gold standard for the determination of intrahepatic lipids (IHCL), fat-water-imaging sequences - Dixon and in particular multi-echo-versions – provide also excellent and spatially resolved results. Techniques to measure intramyo-cardiocellular lipids (ICCL) are demanding and not yet established in many places. Whole-body composition is an established MRI modality which is successfully used to follow the effect of interventions.

Muscular tissue contains two different types of lipid stores, intra- (IMCL) and extra- (EMCL) myocellular lipids which are rather different in many aspects ([1] and refs therein). Thanks to their physical characteristics (EMCL with plate-like structures vs. IMCL in droplets), it is possible to distinguish the two depots in ^{1}H-MR spectra. Since IMCL are related to IR, ^{1}H-MRS became a valuable alternative to muscle biopsies with subsequent histological or electron-microscopic determination. In studies on IR in skeletal muscle, the ^{1}H-MRS based determination of IMCL is among the most frequently used in vivo methods. In particular dietary interventions or lifestyle changes with multiple determinations of IMCL are now done with help of ^{1}H-MRS wherever available.
One remaining problem in the determination of IMCL is the separation of the large EMCL resonance from the much smaller IMCL signal, in particular in obese subjects who would be among the most interesting groups for studies of IR. Methods such as spatially highly resolved chemical shift methods and/or two-(spectral)-dimensional spectroscopy [1,15,41] are developed to overcome these limitations and to give insight into lipid composition.

Multinuclear MRS has been used to investigate the uptake of glucose and the synthesis of muscular glycogen ([2] and refs therein). These experiments are nicely showing the possibilities that are generated by the combination of various nuclei, in particular ^{13}C- and ^{31}P-MRS.

^{31}P-MRS saturation transfer is an elegant method to estimate the flux through biochemical reactions [42-48], e.g. creatine kinase or ATP synthase. While these methods have been used to determine mitochondrial activity - based on the fact that the aerobic synthesis of ATP is located in these organelles – it has been argued that it is also influenced by the activity of ATP synthase in the glycolytic pathway, thus reducing the specificity but not necessarily a potential clinical significance.

Two MRS methods are more specific for mitochondrial activity, the infusion of ^{13}C-labeled substances with an observation of ^{13}C-glutamate following the flux through the TCA-cycle and the recovery of ^{31}P-phosphocreatine (^{31}P-PCr) after exercise. While PCr-recovery is a widely used MRS-method in other diseases and physiological conditions of the musculoskeletal system (see refs in [2]), it is much less applied in IR [49-51]. Higher magnetic fields with increased signal-to-noise allow nowadays at reduction of selected volumes and thus muscle specific observation [52,53]. The application of labeled substances is a very powerful technique, however, requires a lot of experience and generates considerable costs.

Infusion of hyperpolarized ^{13}C-substances has been strongly promoted for imaging purposes, e.g. the visualization of the ischemic heart wall etc. Beside these applications, hyperpolarized substances are also metabolized and can be used to determine the effect of IR, so far mostly in the liver and the heart [54-57].

MRI and in particular MRS are well suited to study the effect of IR on various organs. In the musculoskeletal system, biopsy is an alternative with additional information content, e.g. molecular biology examinations of the tissue. Nonetheless, the non-invasiveness of MR is a strong argument in particular for repeated measurements. In other organs than skeletal muscle such as liver or heart, MR has even more valuable arguments in the competition with biopsy which is limited to severe clinical situations. Further development of non-invasive MR methods for studies of IR is crucial yet it is not sufficient. Another obstacle for the application of MRI and MRS in studies of IR is the fact that the involved clinicians in endocrinology, diabetology, hepatology, sports medicine, and many other clinical specialties usually have no MR system available. Therefore, it is mandatory that radiological and biomedical MR groups support these clinicians methodologically in the application of MRI/MRS in collaborative studies of IR.

Reviews and selected recent papers:

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