Chemical shift selective LASER and SI for optimized detection of Boronophenylalanine (BPA)

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Background: Boronophenylalanine (BPA) is used as ^{10}B-carrying compound in Boron neutron capture therapy (BNCT). For increased water solubility, it is usually administered in a complex with fructose (BPA-F). The ability to detect and map the distribution of this compound non-invasively in patients could significantly improve the safety and clinical efficacy of BNCT. It was previously suggested to use localized ^{1}H MRS for this task, and spectra from phantoms and a single spectrum form a patient, using standard PRESS and STEAM were published (1,2). The aromatic ring protons in BPA are scalar-coupled, so that short-TE sequences are important for detection with optimum sensitivity and minimal phase distortion.

Specific aims: 1) To implement and validate MRS and SI sequences that should provide the highest possible sensitivity for the detection of BPA, while retaining sufficient robustness and spectral quality to enable undistorted phased spectra, automated processing for metabolite maps, difference spectroscopy and SI, and absolute quantification. 2) To demonstrate the first localized *in-vivo* detection of BPA by ^{1}H NMR in animal models.

Methods: The pulse sequences implemented for single-voxel MRS and slice-selective SI are shown in Fig's. 1 and 2. CHESS water suppression (WS) preceded both sequences, and OVS was used with SI. The sequences combine spatially selective refocusing using the LASER approach (3) with chemical-shift-selective excitation of the aromatic proton region using the E-BURP2 pulse shape (4). This pulse excites spins over a selected bandwidth with practically uniform phase, which makes it possible to use relatively long pulses (for narrowband excitation) without a concomitant delay in TE. 10 ms long E-BURP2 and 2 ms hyperbolic secant pulses were used for excitation and refocusing, respectively. For MRS the inter-echo delay (τ_{CP}) was 4.6 ms, and for SI, TE=12.1 ms. BPA images were obtained with 4.5 mm slice thickness, 4.5 cm FOV, and 32x32 spatial matrix. Experiments for obtaining water reference data were conducted separately, without WS and with the excitation band focused on the water. Absolute quantification of BPA by comparison to the water intensity was validated in phantoms. The integrated signal intensity ratios measured for the phantom were used to calculate *in-vivo* BPA concentrations, taking into account the differences in relaxation times. The experiments were conducted with a horizontal-bore 4.7 T spectrometer (Bruker Biospec, Ettlingen, Germany). For *in-vivo* detection, mice were anesthetized with N_2O/O_2/Isoflurane and infused (in the magnet) via the tail vein with a 0.26 M BPA-F solution. A total of ~ 1 ml was injected over ~ 1hr. MRS and SI detection was targeted to one of the kidneys, and spectra and images collected before, during, and after the injection.

Results: At 4.7 T, the four aromatic protons in BPA can be approximated as a weakly coupled AX spin system. The LASER phantom spectrum (Fig. 3) is sufficiently resolved to distinguish separate resonances from free BPA (f), and the more abundant BPA-F complex (c). The *in-vivo* spectra were not resolved as well, but revealed nevertheless that most of the injected complex had dissociated into free BPA and fructose. The upper spectrum in Fig. 3 shows the signal from a single 9 µl voxel in the kidney (part of a SI data set), in which the signal from free BPA clearly dominates. The blue curve shows a simulation based on a 4:1 free:complex ratio. Fig. 4 shows a BPA image from a mouse kidney, overlaid on the T_2-weighted anatomic MRI.

Conclusions: Pulse sequences combining narrow-band, chemical-shift-selective excitation and adiabatic, spatially-selective refocusing are optimal for the *in-vivo* detection of the aromatic proton resonances of BPA, and could be suitable for other situations targeting scalar coupled spin systems. The narrow-band excitation, which avoids the water resonance, and the sharp slice profile of the adiabatic refocusing pulses, which minimizes outer-volume signal contamination, contribute to the achievement of distortion-free spectra even for short echo times or inter-echo delays. *In-vivo* MRS and SI in mouse kidney revealed rapid conversion of the BPA-F complex to free BPA. Although the BPA concentrations detected here in kidneys were very high, extrapolation to the lower fields and larger RF coils expected for patients shows that therapeutic levels of BPA in brain tumors (~2-4 mM) should be detectable at useful spatial resolution.

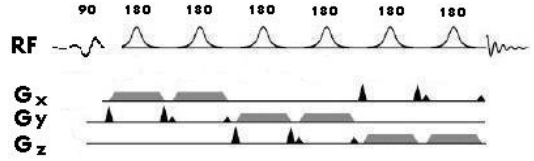

Fig. 1: Pulse sequence for chemical-shift-selective LASER

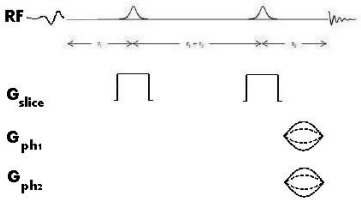

Fig.2: Pulse sequence for chemical-shift-selective, adiabatic refocusing SI

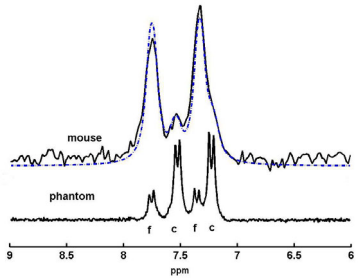

Fig. 3: bottom: LASER spectrum from 0.97 ml voxel in phantom containing 6.5 mM total BPA, 256 scans, TR=1s. Top: spectrum of 9µl voxel in mouse kidney, from 3D SI data, 32x32, TR=1s, LB=2Hz. Dot-dashed line: simulated signal

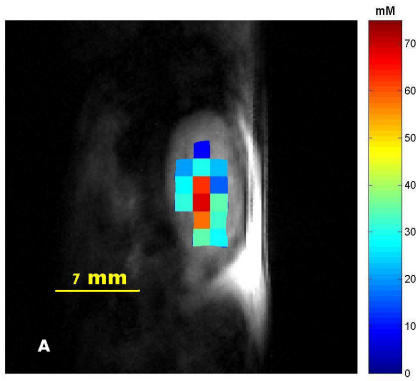

Fig. 4: Concentration map of total BPA (free+complex), derived from an SI experiment, acquired for 17 min starting 68 min after the begin (18 min after the end) of the BPA injection

References

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