

## Abstract

Magnetic resonance imaging and spectroscopy is based on the phenomenon of nuclear magnetic resonance, which has a limited sensitivity because of the small energy difference between the excited and ground state, with energy differences in the radio frequency range. Hydrogen based magnetic resonance imaging looks only at protons in the brain, but there are many other MRI active nuclei that could be measured. The aim of the project is therefore to expand the possibilities of small animal magnetic resonance imaging, in relation to neuroscientific applications, by developing and optimizing X-nuclei magnetic resonance imaging and spectroscopy for in vivo measurements and testing a novel contrast agent based on paramagnetic chemical exchange saturation transfer. Our focus is on two X-nuclei lithium-7 and phosphorus-31. Lithium is the gold-standard in the treatment of bipolar disorder and has been on the market for over 50 years; however, the mode of action as a mood stabilizer is still unclear. Phosphorus is a crucial part of the cell's energy metabolism with compounds such as ATP and phosphocreatine; furthermore, inorganic phosphate is an important physiological buffer. The property of inorganic phosphate as a buffer is useful in  $^{31}\text{P}$  MRS, because it allows for the measurement of pH. In order to achieve our aim we started by looking at in vitro probes that can be used to optimize the sequences before moving on to study lithium ex vivo and an in vivo phosphorus study. The novel contrast agent is based on paraCEST, paramagnetic chemical exchange saturation transfer, this type of contrast agent only gives contrast when a magnetization transfer sequence is used. We show that lithium can be detected at concentrations of 0.1 mM with scan times less than 1 hour, thus suggesting that an in vivo follow up study is possible. We also demonstrate that after placing a fixed ex vivo brain in lithium chloride for 24 hours, followed by 24 hours in water, lithium is retained in the brain at a higher concentration than the original lithium chloride solution, which suggests lithium binding. We have also demonstrated that the pH of a solution containing inorganic phosphate and phosphocreatine can accurately be measured, just as we demonstrate stable in vivo pH measurements. Furthermore, we prove that in vivo  $^{31}\text{P}$  MRI is possible with a spatial resolution of  $1 \times 1 \times 7 \text{ mm}^3$  and a 30 minutes acquisition time. However, the low resolution of the  $^{31}\text{P}$  MRI illustrates the largest challenge in X-nuclei magnetic resonance imaging and spectroscopy, namely that the signal to noise ratio is low. Lastly, we also demonstrate that a novel paraCEST contrast agent can be detected at low concentrations, around  $1 \text{ mg ml}^{-1}$ . We therefore suggest a continuation of the study on the paraCEST contrast agent.

