In vivo NMR spectroscopy of brain at 3 Tesla : methodological developments for studying animal models of Huntington's disease

The aim of this work was to develop new MR methods dedicated to the exploration of animal models (rat and primate) of Huntington's disease by *in vivo* NMR spectroscopy at 3 Tesla. The first part presents three original methodological developments. First of all, a new method is described to correct the spectrometer frequency on the fly using the intracerebral water signal as a frequency reference. This method allows for acquisition of stable spectra even in presence of a field-frequency drift. Secondly, a new method called Semiselective Proton-Observed Carbon-Edited (SPOCE) is proposed to detect separately and simultaneously the proton signals of [4-^{13}C]glutamate and [3-^{13}C]glutamate, even though these signals overlap at 3 Tesla. This new technique allows for the measurement of ^{13}C labeling kinetics of glutamate carbons 3 and 4 from [1-^{13}C]glucose at intermediate field. The tricarboxylic acid (TCA) cycle rate can be calculated by fitting a metabolic model to these kinetic data. Finally, a new method is dedicated to direct GABA concentration measurement without contamination by macromolecules. These three methodological developments are analyzed in detail, then validated *in vitro* and *in vivo*. The second part of this manuscript describes the first applications of these developments to the 3-NP animal model of Huntington's disease. This disease is characterized by a selective degenerescence of GABAergic neurons in the striatum associated to a dysfunction of energy metabolism. 3-NP intoxication yields similar lesions in animals. A first application shows that NAA is a reversible marker of neuronal dysfunction. A second study focuses on potential neuroprotective effects of creatine. Finally, it is showed that the TCA cycle rate is reduced by 17% after acute 3-NP intoxication in rats.