Hyperpolarizing Drugs to Determine their Role in Suppressing Epileptic Seizures and Migraine Headaches via MRI

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Introduction

Migraine affects an estimated 10% to 15% of the population with greater or lesser regularity and throughout much of their lifetime.[1] It causes disability, - be it often temporary, - and it strains personal relationships and professional development. Migraine with aura is an inherited disease, often leading to hemiplegia or even loss of consciousness. Until recently, little was known about it scientifically, and its treatment remained mostly empirical. A French, a Dutch, and an Italian group identified gene loci on chromosomes 19 and 1q23 [2]. The latter gene encodes a sodium / potassium pump located in the membrane of neurons. Recently, valproate has been found to supress migraine if administered prophylactically. The reason or mechanism of this phenomenon is still unknown.

Results

In an effort to learn more about the function of valproate, be it to combat epilepsy or supress migraine, we have magnetically labeled simple model compounds for valproate to investigate their diffusion processes and ease of penetration through the blood-brain-barrier using MRI in combination with hyperpolarized contrast reagents. The latter we have generated via Parahydrogen Induced Polarization (PHIP).[3] PHIP causes strong signal enhancement, if homogeneously catalyzed hydrogenations of unsaturated substrates are initiated with parahydrogen (p-H_2). PHIP is a well studied and extensively applied phenomenon[3]. Its applications extend from detecting reaction intermediates and investigations of reaction mechanisms to kinetic studies. It has been shown that PHIP leads to a signal enhancement of up to 10^4 in the proton NMR spectra. The initial proton polarization can be transferred to other nuclei such as ^{13}C and ^{31}P without the application of special pulse sequences,[4] and this effect can be applied to boost the sensitivity of ^{13}C-MRI, which is restrained by the low natural abundance and poor gyromagnetic ratio of this nucleus.[5]

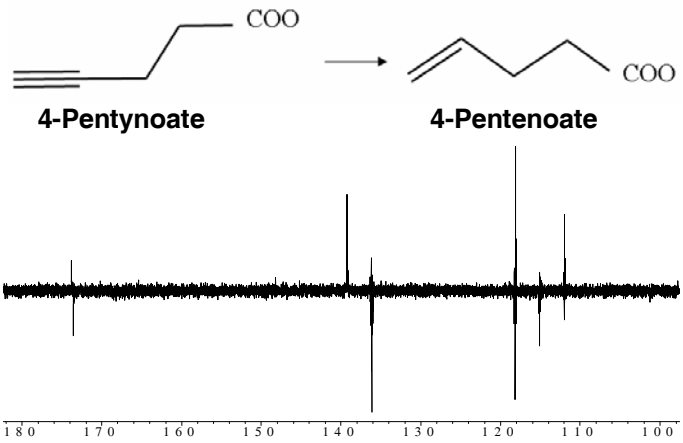

Figure 1: ^{13}C PHIP-spectrum of 4-pentenoic acid

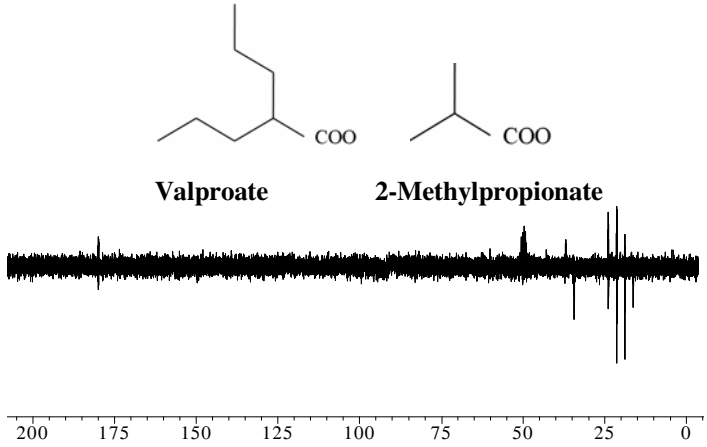

Figure 2: ^{13}C PHIP-spectrum of 2-methylpropionate

Discussion and Conclusion

So far only a few systems have been investigated. We have successfully ^{13}C-hyperpolarized 2-methylpropionate and 4-pentenoic acid, which are both simple models for the target molecules valproate. All shown ^{13}C spectra were obtained after applying a 90° pulse and Fourier transformed only after a single scan. These reactions were conducted within the 4.7 Tesla magnetic field of a 200 MHz NMR spectrometer. For MRI purposes, the reactions have to occur at low field to insure net spin polarization.

More appropriate precursors for valproate are the 2-alkyl-substituted pentenoic acids. Similarly, 2-alkyl-substituted pentynoic acids can be used and parahydrogenated twice. We are currently investigating, which one of the isomeric precursors, namely 2-methyl-4-pentenoic acid or 2-methyl-4-pentenoic acid, transfers the initial proton hyperpolarization most efficiently to ^{13}C, i.e., with the unsaturation either in the middle or at the end of the alkyl chain.

References

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