Hyperpolarizing and Exploring the Function of Drugs Used to Combat Epilepsy via Parahydrogen-Enhanced MRI

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Introduction

In order to treat epilepsy, a number of drugs qualify. Attractive, - from an MRI point of view, - are the structurally related compounds phenobarbital, pirimidon, and ethosuximid, because of their long T_1-relaxation times of the central quaternary carbon atom. To hyperpolarize them using Parahydrogen Induced Polarization (PHIP)[1], suitable precursors are essential.

Already in 1956, Eli Lilly introduced "Methohexital",[2] i.e., 1,5,5-trisubstituted barbituric acids, which contain an acetylenic function Figure 1 outlines their straight-forward syntheses, which start from appropriately substituted malonates. Their parahydrogenation provides access to both ^{1}H- and ^{13}C-hyperpolarized phenobarbitals. Via PHIP-MRI, their penetration of the blood-brain barrier could be studied and their function of in the brain may thus be elucidated.

Conceivably, the corresponding set of barbiturates equipped with a double bond rather than with the triple bond of Methohexital may also qualify as suitable precursors for subsequent parahydrogenation. The choice between the two groups will depend on the side effects associated with them. Ideally, one would like to take advantage of the potential of Methohexital to be parahydrogenated twice. Parahydrogenation of triple bonds yields a higher degree of hyperpolarization and hence a stronger ^{13}C-signal anyway, as has been demonstrated by Golman et al.[3] via ^{13}C-MRI angiography.

Results

We have investigated a variety of unsaturated precursors containing double and triple bonds, among them appropriately substituted derivatives of malonic esters.[4] In this fashion, we have been able to obtain ^{1}H- and ^{13}C-hyperpolarized model compounds similar to the structure of phenobarbital. However, our screening experiments have so far been conducted at high magnetic fields and consequently, they yielded ^{13}C-resonances exhibiting anti-phase-type polarization. To qualify for MRI purposes, the parahydrogenation has to be carried out at low or zero field to obtain net polarization (i.e., all the resonance lines of one and the same resonance have to appear exhibiting only emission or enhanced absorption). We are currently modifying our experimental setup to paraydrogenate at low fields. Thereupon the ^{1}H- and ^{13}C-hyperpolarized phenobarbitals have to be injected into the blood stream. Initially we will attempt to study their speed of penetrating the blood-brain barrier. This can be influenced by modification of the rests $R - R_2$ in Figure 1.

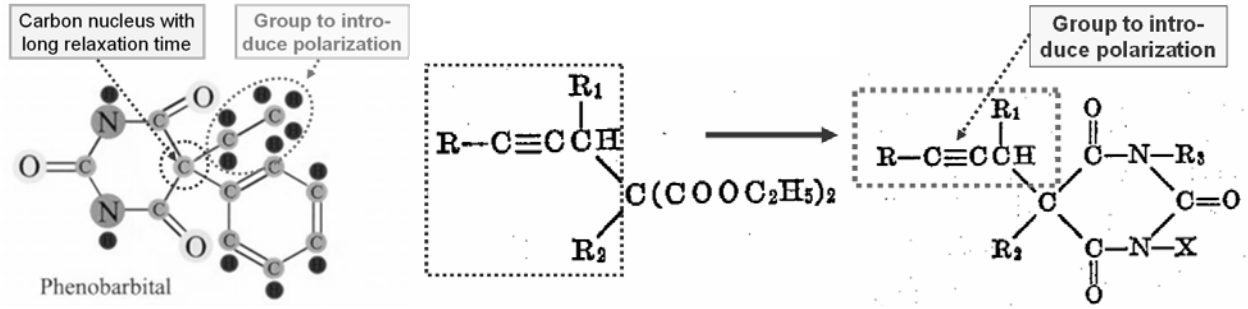

Figure 1: Phenobarbital and the synthesis of the methoxital precursor and related structures from appropriate malonates.

Discussion and Conclusions

Pinpointing the triggers for epileptic seizures in the brain is a prerequisite for their surgical removal and associated treatment of epilepsy. So far, this is not possible reliably enough using non-invasive methods. Accordingly, any progress in increasing the precision of forecasting and identifying the regions of the brain to be removed in a non-invasive way is highly desirable.

References

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