Providing 13C-Hyperpolarized Nicotine Derivatives for Use in 13C-MRI or 13C-MRS

J. Bargon[1], U. Bommerich[2], A. Koch[3], R. R. Rizi[4], M. Roth[3], J. Schmiedeskamp[3], and H. W. Spiess[3]

[1]Institute of Physical & Theoretical Chemistry, University of Bonn, Bonn, Germany, [2]Leibniz Institute for Neurobiology, Magdeburg, Germany, [3]Max-Planck Institute for Polymers, Mainz, Germany, [4]Department of Radiology, University of Pennsylvania Medical Center, Philadelphia, PA, United States

Introduction

Neuronal nicotinic acetylcholine receptors (nAChRs) are a class of ion channels with significant potential as molecular targets for the design of drugs to treat a variety of CNS disorders. The discovery that neuronal nAChRs are further subdivided into multiple subtypes suggests that drugs which act selectively at specific nAChR subtypes might effectively treat Parkinson's disease (PD), Alzheimer's disease (AD), schizophrenia, ADHD, depression, anxiety or pain without the accompanying adverse side effects associated with non-selective agents such as nicotine (1) and epibatidine. Altinicline (SIB-1508Y), a ligand for nAChR, is a small molecule designed to selectively activate neuronal nAChRs and is undergoing clinical evaluation for the treatment of PD. As an unsaturated compound containning a triple bond, it qualifies for in situ hydrogenation using parahydrogen, which yields ^{13}C-hyperpolarized hydrogenation products due to the ParaHydrogen Induced Polarization phenomenon (PHIP).[1] The resulting 5-ethylnicotine is also known to be pharmacologically active, albeit not quite as much as either 6-ethylnicotine or the parent nicotine. The unsaturated precursor for the latter, the 6-ethynylnicotine, qualifies likewise yielding 6-ethylnicotine upon hydrogenation. SIB-1508Y can be synthesized in 5 steps[2] from natural nicotine.

Methods and Results

^{13}C-MRI[3] or -MRS are important diagnostic methods for studying the role of biologically active compounds, but their low sensitivity and the high toxicity of nicotine mandates some form of signal enhancement such as ^{13}C-hyperpolarization derived from PHIP. Accordingly, *in situ* parahydrogenation of the unsaturated altinicline (SIB-1508Y) yields 5-ethylnicotine with up to a 10^5–fold ^{13}C-signal enhancement.

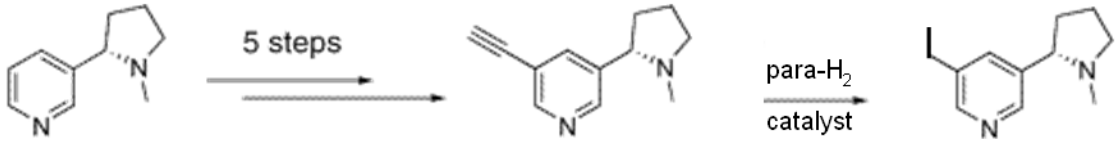

Figure 1: **(S)-nicotine** **SIB-1508Y** **5-ethylnicotine**

^{13}C-hyperpolarized 3-ethylnicotine can be regarded as model compound for ligands that bind to nAChRs, for drugs to combat PD, AD, or ADHD, but it may also serve as a substitute for nicotine to investigate its role in the lung upon inhalation. Since nicotine readily penetrates the blood-brain-barriere, it may also qualify to determine the topographical distribution of nAChRs in the brain as has been studied through various methods: immunohistological and immunoprecipitation experiments, radioligand binding and autoradiographic techniques. However, the subunit composition of functional receptors in different brain areas is an ongoing question.

Discussion and Conclusions

We have ^{13}C-hyperpolarized substituted styrenes starting from the corresponding ethynylbenzenes and parahydrogenating these unsaturated precursors at both high and low magnetic fields. The resulting signal enhancement for ^{13}C gets near the theoretical limit obtainable via Dynamic Nuclear Polarization using microwave pumping in the presence of suitable stable free radicals. Both, the ^{15}N in the pyridine and pyrrolidine rings of the nicotines may likewise be hyperpolarized.

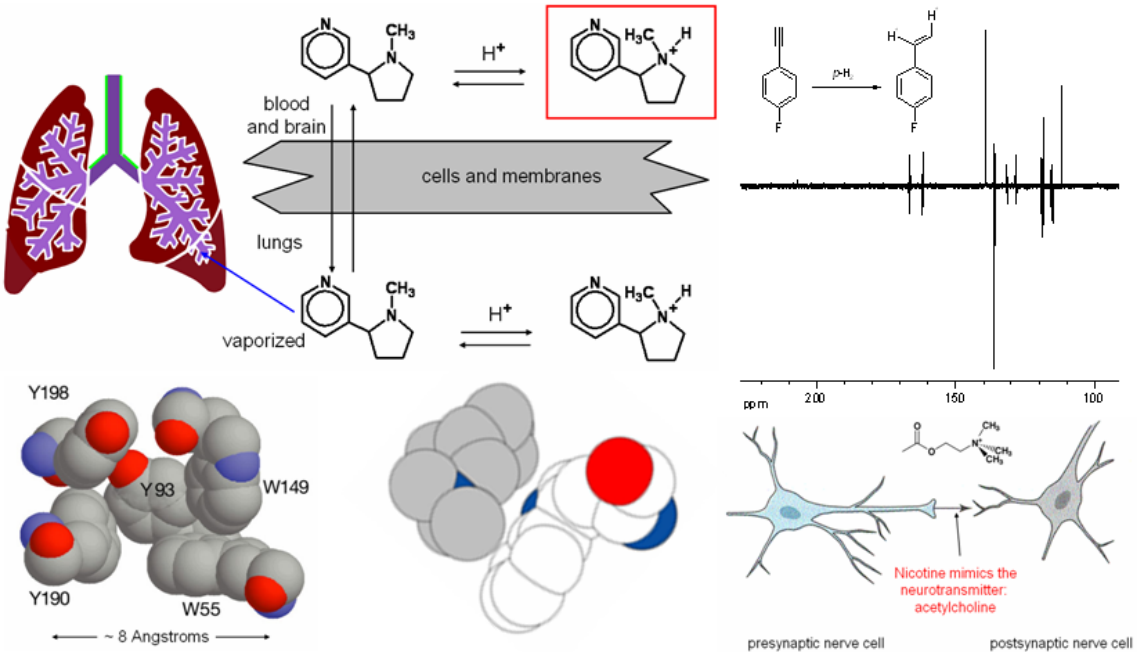

Figure 2: Nicotine on its way from the lung to the brain, ^{13}C-PHIP NMR-spectrum and function.

References

1.) Bowers CR, Weitekamp D, Phys. Rev. Lett., **57**, 2645, **1986**; Natterer J, Bargon J, Prog. Nucl. Mag. Res. Sp. **31**, 293-315, **1997**.
2.) Wagner FF, Comins DL**,** Expedient Five-Step Synthesis of SIB-1508Y from Natural Nicotine, J. Org. Chem. 71, 8673-75, **2006**.
3.) Golman K, Axelsson O, Jóhannesson H, et al. Mag. Res. Med. 46, 1-5, **2001.**