Introduction

Stroke is the leading cause of disability in the United States. Annual stroke incidents amount to approximately 731,000 cases (Broderick et al. 1998) yearly and are the third leading cause of death. A stroke or cerebral vascular event is defined as a sudden neurological deficit in the brain caused by either ischemia (lack of blood supply to the brain) or a hemorrhage: 80% of all strokes occur due to arterial blockage (ischemia), and 20% occur due to bleeding (hemorrhage). The majority of strokes occur when a blood clot blocks the flow of oxygenated blood to a portion of the brain. This type of stroke is called ischemic stroke. Ischemic strokes can be caused by blood clots that form inside the artery of the brain (a thrombotic stroke) or by a clot that forms somewhere else in the body and travels to the brain (an embolic stroke). Ischemic strokes account for 80% of all strokes. Thrombotic strokes are caused by clogged blood vessels upon a build up of various deposits, generally referred to as atherosclerotic disease. A thrombotic stroke can occur in large arteries or cause small vessel disease. The latter occurs when blood flow is blocked to a very small arterial vessel. Little is known about the small vessel disease, but it is often closely linked to hypertension and is an indicator of atherosclerotic disease. - Two different types of drugs are used to combat strokes and to reduce the risk of a second one: Low-dose aspirin is considered first-line therapy for the stroke prevention in those with high risk. - Anticoagulant drugs such as heparin, warfarin (Coumadin), or phenprocoumon (Marcumar) interfere with the initiation of the coagulation cascade and significantly reduce the risk that a blood clot will form. Warfarin is slower acting than the common anticoagulant heparin, though it has a number of advantages. Warfarin, originally developed as a rat poison, is the most widely prescribed anticoagulant drug in the US, yet its true physiological role in the body remains unclear. It is assumed that Warfarin and related coumarins decrease blood coagulation by inhibiting vitamin K epoxidase reductase, an enzyme that recycles oxidated vitamin K to its reduced form after it has participated in the carboxilation of several blood coagulation proteins. Therefore, drugs of this type are also referred to as vitamin K antagonists. Its two active optical isomers are typically used as a racemic mixture of R- and S-forms, each of which is cleared by different pathways. S-warfarin has 5 times the potency of the R-isomer with respect to vitamin K antagonism. Antiplatelet drugs such as Ticlid (ticlopidine) or Trental (pentoxifylline) inhibit platelet aggregation, thereby reducing the risk of a new blood clot forming in the brain. - Furthermore, bronchopulmonary dysplasia is a leading cause of mortality and morbidity in preterm infants despite improved treatment modalities. Pentoxifylline, a phosphodiesterase inhibitor, also inhibits multiple processes that lead to neonatal hypoxic lung injury, including inflammation, coagulation, and edema. Therefore, improving the knowledge of the physiological role of these anticoagulant drugs in the body is very desirable.

Method and Results

$^{13}$C-MRI$^1$ or $^{13}$C-MRS are powerful tools for studying the role of biologically active compounds and of drugs, but the low sensitivity of these methods requires signal enhancement such as $^{13}$C-hyperpolarization derived from DNP or PHIP$^2$. PHIP uses parahydrogenation of suitably unsaturated precursors containing either double or triple carbon-carbon bonds. PHIP yields these products in $^{13}$C-hyperpolarized form due to the Parahydrogen Induced Polarization (PHIP) phenomenon based upon the PASADENA effect. For this purpose the hydrogenations are carried out in situ, preferably at very low magnetic fields. Accordingly, a variety of $^{13}$C-hyperpolarized anticoagulants like warfarin, phenprocoumon, or pentoxifyllin are accessible, a prerequisite for applying $^{13}$C-MRI$^2$ or $^{13}$C-MRS as exploratory methods.

![Figure 1](image1.png)

Accordingly, other anticoagulants, - be it acenocoumarol, naftidrofuryl, or the selective cAMP phosphodiesterase inhibitors cilostazol or tirofiban, - may become $^{13}$C-hyperpolarized, even in the correct chiral form using the corresponding chiral catalyst if required.

![Figure 2](image2.png)

Discussion and Conclusions

$^{13}$C-MRI/MRS in combination with signal enhancement via $^{13}$C-hyperpolarization derived from parahydrogen followed by polarization transfer to $^{13}$C at low magnetic fields represents an attractive alternative to the alternate DNP-based approach, and allows studying the functions of various anticoagulants. In contrast to the DNP-based approach, PHIP can yield $^{13}$C-hyperpolarized substrates continuously.

References