Determinants of magnetization transfer efficiency in tissue and cells

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Introduction: Magnetization transfer (MT) between water and cell lattice (protein and membrane phospholipid) protons has been utilized in MRI imaging to enhance contrast and is a major determinant of the tissue water relaxation time. MT in tissue or cells is best modeled as a multiple-step interaction network that includes cross relaxation (or NOE), spin-diffusion (mutual spin flip-flop due to dipolar coupling) and chemical exchange. The aim of this study is to identify the important factors that determine MT efficiency between water and cell lattice protons.

Methods: HRMAS NMR NOESY experiments were performed on model membranes synthesized from: 1, pure phosphatidylcholine and 2, mixtures of phosphatidylcholine and cholesterol. The rate of direct intermolecular NOE between water and non-labile membrane protons was measured and the role of labile protons in the MT between water and membrane was determined. Theoretical modeling was used to examine the role of a small number of labile protons in the MT between water and membrane. Finally, MT experiments were performed on fresh muscle samples and theoretical modeling was used to assess the saturation of cell lattice based on the relation of the irradiation power intensity to the magnitude of residual dipolar coupling in membrane phospholipids and proteins.

Results: Intermolecular NOE experiments on the model membranes reveal that in the absence of cholesterol the direct intermolecular NOEs between water and membrane protons are typically weak negative peaks (**Fig. 1a**). With 1:1 cholesterol:phosphatidylcholine, the intermolecular NOEs between water and all membrane protons are strong positive peaks (**Fig. 1b**). These experiments demonstrate that direct intermolecular NOE between non-labile protons and water is negligible and show the crucial role of cholesterol hydroxide in enhancing the MT between water and membrane protons. Cholesterol hydroxide exchanges with water with a time constant of ~ 1 ms (**Fig. 2**). The ratio of cholesterol hydroxide to membrane protons or water protons is less than 1:80 but still results in efficient MT between water and membrane protons. Theoretical modeling confirms that a small number of labile protons can foster a significant MT between a much larger pool of water and cell lattice protons when the exchange time constant of labile proton and water is in the ms range, which warrants both a fast exchange between water and labile protons and a rapid flip-flop spin diffusion between labile protons and cell lattice. MT experiments on fresh muscle show that the saturation of cell lattice protons and MT are power dependent (**Fig. 3**). When the irradiation power is much smaller than the residual dipolar coupling, it can barely saturate the cell lattice protons, which is consistent with the Provotorov theory[1]. This low power irradiation results in very low levels of MT from cell lattice to water protons; but is still able to saturate the labile protons and induce chemical exchange contrast. An irradiation power of more than 400 Hz can rapidly saturate the cell lattice and induce large MT from the cell lattice to water protons, which is consistent with the Redfield theory at high field[2].

Conclusions:

1. Direct NOE between water and non-labile protons of the cell lattice is weak and negligible in a MT network.
2. A very limited number of labile protons can foster significant MT between water and non-labile protons.
3. Exchange between water and labile protons is the major factor in determining the MT rate of the whole system.
4. Saturation of the cell lattice determines the degree of magnetization reduction of water due to MT and is dependent on the relative intensity of the irradiation pulse and residual dipolar coupling in tissue.

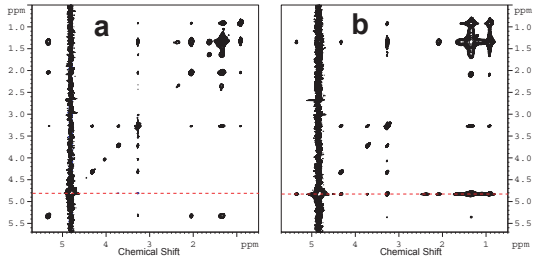

Fig. 1. 2D NOESY of model membrane of phosphatidylcholine (**a**) and 1:1 phosphatidylcholine and cholesterol (**b**). Dashed red line shows the NOE cross peaks between water and membrane protons.

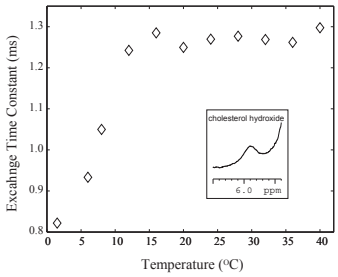

Fig. 2. Exchange time constant of cholesterol hydroxide with water in model membrane. Inset is the cholesterol hydroxide in NMR spectrum.

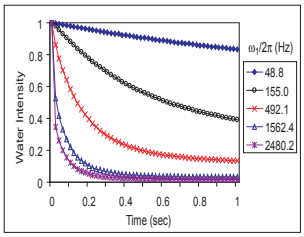

Fig. 3. Satuation of water signal using saturation pulse at 8.3 ppm with different pulse length on a fresh muscle sample.

Reference:

1. B. N. Provotorov. Soviet Phys. 112, 837 (1955). 2. A. G. Redfield. Phys. Rev. 112, 837 (1958).