Magnetic Resonance Methods and Applications in Pharmaceutical Research

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ABSTRACT: This review presents an overview of some recent magnetic resonance (MR) techniques for pharmaceutical research. MR is noninvasive, and does not expose subjects to ionizing radiation. Some methods that have been used in pharmaceutical research MR include magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) methods, among them, diffusion-weighted MRI, perfusion-weighted MRI, functional MRI, molecular imaging and contrast-enhance MRI. Some applications of MR in pharmaceutical research include MR in metabonomics, *in vivo* MRS, studies in cerebral ischemia and infarction, degenerative joint diseases, oncology, cardiovascular disorders, respiratory diseases and skin diseases. Some of these techniques, such as cardiac and joint imaging, or brain fMRI are standard, and are providing relevant data routinely. Skin MR and hyperpolarized gas lung MRI are still experimental. In conclusion, considering the importance of finding and characterizing biomarkers for improved drug evaluation, it can be expected that the use of MR techniques in pharmaceutical research is going to increase in the near future. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:3637–3665, 2008

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INTRODUCTION

Magnetic resonance is recognized as one of the most important medical advances of the 20th century. It has opened new windows into the human body, revealing structure and function with a level of detail that would have been unimaginable only decades ago.

The phenomenon of nuclear magnetic resonance (NMR) has been known since the end of the 1930s, when nuclear magnetism was detected by Lasarew and Schubnikow.[1] However, the discovery reported in 1946 by Bloch,[2] Bloch et al.,[3] and Purcell et al.[4] is internationally recognized as the birth of this technique, which gave way to numerous studies on the quantum mechanical properties of an atom's nucleus. This work resulted in the joint award of the Nobel Prize

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for Physics in 1952 to Felix Bloch and Edward Purcell. NMR studies magnetic nuclei by aligning them with a very powerful external magnetic field and perturbing this alignment using an electromagnetic field. The resulting response to the external perturbing electromagnetic field is the phenomenon that is exploited in NMR spectroscopy and magnetic resonance imaging (MRI). A relatively new technique that can provide a real breakthrough in the field combines MRI technology with scanning probe microscopy to obtain images somewhat like those obtained by MRI but on a much smaller scale.[5] However, the final impact of this so-called magnetic resonance force microscopy for the study of live tissues is still speculative.

New technical advances and developments in NMR spectroscopy (or simply, magnetic resonance spectroscopy, MRS) as well as in functional and molecular MRI are responding to the demands of modern drug development for improved biomarkers providing information on drug interactions at specific molecular targets and for pharmacological endpoints. Our main objective in this review is to describe some of the MRI and MRS techniques used in biomedical and pharmaceutical research, and to present some of their applications.

MAGNETIC RESONANCE METHODS

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a unique tool for biomedical research, which provides biochemical information. Traditionally, this information has been obtained through high-resolution MRS of cell suspensions, cellular and tissue extracts, and through the more physiologically relevant techniques of perfusion of cells and organs. However, MRS studies can also be carried out *in vivo*. For pharmaceutical sciences, MRS offers the possibility of investigating the concentration and distribution of certain drugs administered at high concentrations, for example, for cancer therapy, as well as of examining drug effects by providing biochemical information. MRS of different magnetic nuclei such as ^{1}H, ^{7}Li, ^{19}F, ^{31}P, or even enriched ^{13}C or ^{195}Pt of Platinum complexes[6] is feasible. As a general remark, broadening of the lines from spectra acquired *in vivo* or *ex vivo* (from perfused organs or tissues) is an important aspect to take into account. Results from high-resolution studies performed on fluids or solutions of chemical extracts may be dependent on the applied extraction procedures; moreover, the process is time consuming and can introduce significant bias between spectra of intact tissues and tissue extracts prepared with different solvents. Alternatives such as increasing echo times or reducing voxel sizes in *in vivo* MRS experiments can result in significant signal losses. Finally, resolution may be improved by increasing the external magnetic field for *in vitro* or *ex vivo* studies. However, for *in vivo* applications, artifacts due to magnetic susceptibility may result in limited applications to very homogenous regions of the body. For *in vivo* MRS, the use of surface coils that can be positioned close to the region of interest or the use of special pulse sequences including variable gradients superimposed on the magnetic field provide precise location of what region or regions of the body the instrument is measuring. Localized MRS offers also the option of an image based on a particular chemical shift. This technique, also called spectroscopic imaging, will benefit from continuous developing in detection sensitivity, improved software for data processing, and reduced scan times from reduced phase encoding strategies similar to those that are being developed for parallel MRI.

Magnetic Resonance Imaging

Magnetic field gradients can be used to encode the spatial position of spins in a sample. That encoding can be inverted and therefore, an image of the sample is obtained. This is known as magnetic resonance imaging (MRI).

MRI most typically produces two-dimensional (2D) and three-dimensional (3D) images. Acquiring several 2D slices of an object may seem equivalent to 3D, but the former needs shorter acquisition time and presents lower signal to noise ratio (SNR) than the latter (and, of course, reconstruction is performed differently). An MRI image can have any orientation, and spatial resolution or field of view do not need to be isotropic (i.e., do not need to be the same in all directions). Spatial resolution in MRI does not depend on the wavelength of the RF fields, and, within limits imposed by the imaging hardware and the physical properties of the sample, can take any value.[7,8]

Other imaging techniques widely used are radiography, fluoroscopy, computed tomography