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Fatty Acids as a Concept for Probes in Cardiologic PET/MR Imaging

TO THE EDITOR: The June supplemental issue of *The Journal of Nuclear Medicine* reflects and enhances skillful developments in the merging of PET and MR imaging according to the existing status of qualified use. That, in particular, holds for cardiology, as Osman Ratib and René Nkoulou present applications, potential, and the need for PET/MR imaging with the challenging aim of having not just a fusion of two imaging systems but a true synergic benefit (*1*). One masterpiece illustration of the strong and unique power of the PET method in cardiology was a 1999 study by a coeditor of the supplement, Markus Schwaiger, and his group proving the phenomenon of reinnervation in transplanted hearts by use of ^{11}C-hydroxyephidrine and PET (*2*). That is one type of PET application by which PET/MR imaging can open new doors in diagnostic cardiology.

Among various important issues, Osman Ratib and René Nkoulou point out the need for methods to assay myocardial viability, for which PET, indeed, offers substantial possibilities. This need can clearly be understood in the case of coronary artery disease, for which localization and qualification of a stenosis are the first diagnostic steps in a line toward deciding therapeutic strategies to normalize blood flow. Yet, the final question is the effect of coronary artery disease and subsequent therapy on the metabolic situation, as the authors characteristically address with the term *viability,* and possible mismatch between perfusion and metabolism, in general, has to be taken into clinical consideration (*3*).

In that context, we would like to draw attention to the key role of myocardial metabolism in meeting the energy demand of the working heart. This role offers an approach for assaying the viability of the heart muscle. Fatty acids are the main source of energy for metabolism, meeting the instantaneous demand for energy by the myocardium by producing adenosine triphosphate (ATP) as the general fuel for all metabolic reactions and physiologic functions within the organ. In myocardium, ATP is stored in only small amounts, if at all, and therefore has to be formed instantaneously when needed. Within the metabolic turnover, one molecule of palmitic acid results in the formation of 131 molecules of ATP. In the case of glucose, as the second substrate for energy supply, 36 molecules of ATP are formed. Therefore, fatty acids offer the basis for valuable PET probes to assay myocardial viability, and in particular, PET/MR imaging now appears to pave new ways in cardiology by integrating the tracer method using fatty acids labeled with PET radionuclides.

This letter also is being written to recall work with aliphatic and phenyl fatty acids that were radioiodinated and applied in experimental and clinical studies. Both groups of compounds can be prepared with PET radionuclides. ^{11}C-palmitic acid is considered to exhibit some logistic disadvantages; in contrast, 16-^{18}F-palmitic acid is readily obtained by standard radiofluorination protocols and, most interestingly, is known to have a physiologic behavior similar to that of ^{11}C-palmitic acid despite the fluoride substituent (*4*). 15-phenylpentadecanoic acid (PPA) radioiodinated at the benzene ring is efficiently labeled by ^{11}C (*5*). The beneficial aspect of PPA is that β-oxidation results in the release of labeled benzoic acid, which can be used for quantification of the oxidative degradation (*6*). In the past, those structures were modified by various substitutions or insertions into the carbon chain to block or delay metabolic turnover, as blocking was thought to be advantageous just for SPECT imaging (*7*). Radioiodinated PPA was experimentally shown to have a metabolic pathway resembling that of palmitic acid. Most important, among various clinical applications iodophenylpentadecanoic acid was proven to normalize energy metabolism after revascularization (*8*). Furthermore, a modeling approach allows quantification, which may be useful in other therapeutic strategies (*9*). PPA allows direct tracing of both essential metabolic paths: oxidative turnover within β-oxidation and storage in lipids and glycerides.

Because of their general role in energy metabolism, fatty acids do not compete with ^{18}F-FDG as probes for myocardial viability. Although ^{18}F-FDG has a role as a PET probe in cardiology, Osman Ratib and René Nkoulou correctly remind us to the limitations of ^{18}F-FDG as a PET probe.

In summary, fatty acids labeled with PET radionuclides can be considered valuable probes for assay of myocardial viability and may represent a strong tool when PET is merged with cardiologic applications of MR imaging.

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PET Imaging of Adenosine A_1 Receptor Occupancy

TO THE EDITOR: We have recently published 2 articles about the use of ^{11}C-MPDX (8-dicyclopropylmethyl-1-^{11}C-methyl-3-propylxanthine) and PET for measurement of adenosine A_1 receptor occupancy by nonradioactive agonists and antagonists (*1,2*). Dose-dependent occupancy of A_1 receptors in the rodent brain by antagonists (caffeine, DPCPX [1,3-dipropyl-8-cyclopentyl xanthine]) could be assessed, but administration of an exogenous agonist (CPA [N^6-cyclopentyladenosine]) or raising the levels of endogenous adenosine by treating animals with ethanol and the adenosine kinase inhibitor ABT-702 (4-amino-5-(3-bromophenyl)-7-(6-morpholino-pyridin-3-yl)pyrido[2,3-d]pyrimidine) did not result in measurable competition of agonist and tracer. A paradoxic increase of tracer uptake was observed under these conditions. Kinetic modeling of the PET data suggested that there was an increase in tracer binding potential rather than in tracer delivery to the brain or passage of the tracer across the blood–brain barrier. This phenomenon was unexpected and could not be explained.

At the recent Purines 2014 meeting in Bonn, a possible explanation was offered by Drs. Andreas Bauer (Düsseldorf, Germany) and Renata Ciccarelli (Chieti, Italy). These experts pointed out that many ligands for adenosine A_1 receptors that initially were considered antagonists are in fact inverse agonists. Inverse agonism has been proven for WRC-0571 (8-(*N*-methylisopropyl) amino-N^6-(5′-endohydroxy-endonorbornyl)-9-methyladenine) (*3*), CGS-15943 (9-chloro-2-(furan-2-yl)-[1,2,4]triazolo[1,5-c]quinazolin-5-amine) (*3*), DPCPX (*3*), and CPFPX (8-cyclopentyl-(3-(3-fluoropropyl)-1-propylxanthine) (*4*). The last 2 ligands are structurally similar to our tracer, MPDX.

Inverse agonists such as DPCPX display a high affinity for the uncoupled, or inactive, state of the A_1 receptor and a lower affinity for the G-protein–coupled state (*5*). Paradoxic increases in ^{11}C-MPDX binding in the rodent brain on administration of CPA or treatment of rats with ethanol and adenosine kinase inhibitor may therefore be explained in the following way: agonists (such as CPA or adenosine) increase the fraction of A_1 receptors in the uncoupled state, because the ternary complex consisting of agonist, activated receptor, and G-protein is not stable in living tissue. Guanosine triphosphate binding results in decoupling of the G-protein from the complex and relaxation of the receptor to the inactive conformation, possessing low affinity for the agonist but high affinity for an inverse agonist such as ^{11}C-MPDX. Thus, the binding potential for ^{11}C-MPDX is increased after administration of a pharmacologic dose of an agonist. An increase (23%–55%) similar to that we observed for ^{11}C-MPDX binding in the rodent brain after agonist treatment was seen for ^{3}H-DPCPX binding in human brain slices on the addition of guanosine triphosphate (*6*).

This hypothesized explanation of our PET findings could be tested by radiolabeling a neutral antagonist and repeating the experiments with that tracer. Binding of an antagonist tracer should not be increased in the presence of an excess of agonist, in contrast to binding of an inverse agonist such as ^{11}C-MPDX or ^{18}F-CPFPX. To achieve this goal, a neutral antagonist with nanomolar affinity should be developed that is amenable to labeling (*7*). It may also be possible to use the nonxanthine PET tracer ^{11}C-FR194921 (^{11}C-2-(1-methyl-4-piperidinyl)-6-(2-phenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (*8*).

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