Synthesis and preliminary evaluation of [1-\(^{11}\)C]hexanoate as a PET tracer of fatty acid metabolism

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The potential of [1-\(^{11}\)C]hexanoate (\(^{11}\)C-HA) as a radiopharmaceutical assessing fatty acid metabolism of the myocardium and brain tissues by PET studies was evaluated. \(^{11}\)C-HA was synthesized by the Grignard reaction of pentylmagnesium bromide and \(^{14}\)CO\(_2\). \(^{11}\)C-HA, [1-\(^{14}\)C]acetate and \([\text{H}]\)deoxyglucose were simultaneously injected i.v. into mice, and the tissue distribution of the three radionuclides was measured. In the heart, high uptake and rapid clearance of \(^{11}\)C and \(^{14}\)C was found. The brain uptake of \(^{11}\)C was twice as high as that of \(^{14}\)C, and both \(^{11}\)C and \(^{14}\)C decreased slowly compared to the heart. The level of \(^{3}\)H increased with time in both the heart and brain. In fasting conditions, the uptake of \(^{11}\)C by the heart was enhanced and the level of \(^{3}\)H decreased with time. The brain uptake of \(^{11}\)C and \(^{3}\)H was also enhanced. The fasting conditions did not affect the distribution of \(^{14}\)C. The radiation absorbed dose of \(^{11}\)C-HA was also estimated.

**Key words:** [1-\(^{11}\)C]hexanoate, heart, brain, oxidation, PET

INTRODUCTION

Radioabeled fatty acids have been used to determine the myocardial metabolism.\(^1\)\(^2\) In positron emission tomography (PET), carboxyl-[\(^{11}\)C]-labeled long straight-chain fatty acids are used as a probe to measure the rate of \(\beta\)-oxidation of fatty acids in the heart, in which high extraction and rapid clearance of the radioactivity was found. On the other hand, \(\beta\)-methylated fatty acids are expected to be resistant to \(\beta\)-oxidation and to be retained in the heart.\(^6\)\(^9\) In contrast to \(\beta\)-methyl fatty acids, \(\alpha\)-methyl fatty acids are not resistance to \(\beta\)-oxidation. Therefore, no attention has been paid to the application of the \(\alpha\)-methyl fatty acids as a tracer of fatty acid metabolism.

It is considered that glucose is the only fuel in the brain and that fatty acids are not an energy source, but mitochondria in the brain have ability to oxidize fatty acids.\(^11\) The \(\beta\)-oxidation process of the fatty acids in the brain may play a role in regulating lipid metabolism. When radioabeled long-chain fatty acids such as palmitate were injected into rats, a part of the radioactivity in the brain was incorporated into the lipid fraction and the rest became water-soluble materials probably via the \(\beta\)-oxidation process.\(^12\)\(^13\) On the other hand, a short chain fatty acid octanoate was scarcely incorporated into the lipids and its major metabolites were glutamate and glutamine in the rat brain.\(^14\)

Recently, Ogawa et al. synthesized radioabeled \(\alpha\)-methyl fatty acids with carbon-chain length C\(_3\) to C\(_6\) by malonic ester synthesis.\(^15\)\(^16\) They found that \(\alpha\)-[\(^{14}\)C]methylated short-chain fatty acids and [3-\(^{14}\)C]propionic acid were taken up by the brain and the level of radioactivity was retained for a while. The highest brain uptake was observed in C\(_6\) form, \(\alpha\)-methyl hexanoic acid (MHA). When MHAs labeled at two different sites, \(\alpha\)-methyl and carboxyl \(^{14}\)C-labeled MHAs, were administered to mice, the time-radioactivity curves for the two compounds in the brain were quite different. The level of radioactivity of the [methyl-\(^{14}\)C]MHA in the brain increased for the first 20 min, then decreased gradually, whereas that of [1-\(^{14}\)C]MHA decreased rapidly with time after the injection similar to straight-chain [1-\(^{14}\)C]hexanoic acid. This contrast in the time-radioactivity profile corresponded closely to the difference between [3-\(^{14}\)C]propionic acid and [1-\(^{14}\)C]propionic acid. The level of the radioactivity of the [methyl-\(^{14}\)C]MHA was even higher than that of the [3-\(^{14}\)C]propionic acid. We considered that the short-chain...
fatty acids taken up by the brain were degraded through β-oxidation in the same way in the myocardium, then further metabolized to 14CO2.

In this study, we synthesized straight-chain [1-13C]hexanoate (13C-HA), and investigated its potential as a radiopharmaceutical for assessing metabolism in the heart and brain by PET. α-Methyl fatty acids are degraded by β-oxidation to propionyl-CoA, which is altered to succinyl-CoA by three successively enzymic reactions and enters the tricarboxylic acid cycle. On the other hand, straight-chain fatty acids become acetyl-CoA by the β-oxidation, which directly enters the tricarboxylic acid cycle. Fatty acids labeled with a carbonylic group are preferable for the kinetic analysis by PET, because the radioactivity taken up by the heart and brain could disappear depending on the oxidative metabolism via the tricarboxylic acid cycle in the tissues. Since 2-deoxy-2-[14F]fluoro-D-glucose and [1-13C]acetate are currently used as metabolic radiopharmaceuticals for PET studies, the potential of 13C-HA was investigated compared with [1H]deoxy-D-glucose (1H-DG) and [1-13C]acetate (13C-AA) in normo- and fasting mice.

MATERIALS AND METHODS

Materials

1H-Deoxy-D-glucose (specific activity of 392 GBq:mmol) and sodium [1-13C]acetate (specific activity of 2.11 GBq/mmol) were purchased from Amersham International plc (England). Pentylmagnesium bromide (2.0 M solution in diethyl ether) was specially packed in Sure/SealTM bottles purchased from Aldrich Chemical Co. Inc. NEFA C-test Wako for measuring nonesterified free fatty acids (NEFA) in the plasma was purchased from Wako Chemical Industries Ltd.

Synthesis of sodium [1-13C]hexanoate (13C-HA) [13C]Carbon dioxide was produced as described previously.17,18 The [13C]CO2 trapped in the copper tube was transferred with a flow of 10 mL/min into 0.2 mL of 2.0 M pentylmagnesium bromide in diethyl ether at 40–50°C in a CH2OH bath cooled with liquid N2. After the carboxylation, 1 mL of 1.0 M HCl was added into the reaction mixture, which was extracted with 2 mL of diethyl ether. The ether phase was added into 1 mL of 7% (0.875 M) NaHCO3, then the solution was evaporated to dryness to remove radioactive and non-radioactive volatile materials. The residue was dissolved in physiological saline and the 13C-HA solution was passed through a 0.22 µm membrane filter.

The radiochemical and chemical purity of the 13C-HA were analyzed by high-performance liquid chromatography (HPLC). HPLC conditions: column, eluent, flow rate, temperature and retention time of HA: were: Aminex Fermentation Monitoring column (7.8 mm x 150 mm, Bio-Lad), H2O, 1.0 mL/min, 65°C and 14.0 min; and Partisil 10 SAX (4.0 mm x 250 mm, Whatman), 10 mM NaH2PO4, 2 mL/min, 40°C and 2.8 min.

Biodistribution studies

Two groups of eight-week-old male ddY mice were used. The first group of mice was allowed free access to food and water (the control group), and the other group of was given only water for 1 day before the experiment (the fasting group).

A set of control mice were intravenously injected with 13C-HA (8.0 MBq), then killed by cervical dislocation at 5, 15, 30, 60 and 90 min post injection. Blood was removed by heart puncture with a heparinized syringe and the organs were dissected. The samples were counted for 13C in a gamma-counter, and weighed. The tissue uptake of radioactivity was expressed as % injected dose per g tissue. Radiation dosimetry was estimated as described previously.19,20

Another set of control mice and the fasting mice intravenously injected with a mixture of 13C-HA (4.0 MBq), 1H-DG (1.5 kBq) and 13C-AA (1.5 kBq) were killed by cervical dislocation at 1, 3, 5, 10, 15, 30 and 60 min post injection. Blood was removed as described above, and centrifuged to obtain plasma. The heart and brain were dissected and divided into two portions. A part of the heart and cerebral cortex (about 50 to 100 mg) and 20 µL of plasma were dissolved in the tissue solubilizer and counted for 1H and 13C in a liquid scintillation counter after the decay of 13C radioactivity. The rest of the tissues and plasma were counted for 13C. The tissue uptake of radioactivity was expressed as the % injected dose per g of tissue. Concentrations of glucose and NEFA in the plasma were measured in a Clinical Chemistry Analyzer (CL-760, Shimadzu) and with a NEFA C-test Wako kit (a method using acyl-CoA synthetase and acyl-CoA oxidase), respectively.

RESULTS

13C-HA was synthesized by the Grignard reaction. The yield of carboxylation of pentylmagnesium bromide with 13CO2 was dependent upon the flow rate of 13CO2 and temperature. When 13CO2 was introduced into the pentylmagnesium bromide solution at 40–50°C at 10 mL/min, the slowest flow rate in our system, followed by HCl hydrolysis, 42.1% (mean of 4 runs, ranging of 35.0% to 49.6%) of the total 13CO2 was reacted to the carboxylation. At 16°C and 0°C in the carboxylation, the yields were 30.2% and 17.6%, respectively. Over 94% of the radioactivity in the reaction mixture was detected as 13C-HA. Undesirable radioactive and nonradioactive materials, including pentane derived from the pentylmagnesium bromide, were removed by evaporation of the solution to dryness. The decay-corrected radiochemical yield was 27.9% (mean of 4 runs, ranging of 24.9% to 32.5%) based on the [13C]CO2 used. The HPLC analysis showed radio-
Table 1  Tissue distribution of radioactivity in mice after intravenous injection of $^{11}$C]hexanoate

<table>
<thead>
<tr>
<th>% injected dose/g tissue*</th>
<th>5 min</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>1.67 ± 0.09</td>
<td>0.93 ± 0.07</td>
<td>0.68 ± 0.07</td>
<td>0.46 ± 0.07</td>
<td>0.29 ± 0.03</td>
</tr>
<tr>
<td>Brain</td>
<td>2.28 ± 0.32</td>
<td>1.37 ± 0.13</td>
<td>1.01 ± 0.06</td>
<td>0.48 ± 0.05</td>
<td>0.35 ± 0.03</td>
</tr>
<tr>
<td>Heart</td>
<td>2.12 ± 0.16</td>
<td>1.37 ± 0.16</td>
<td>1.03 ± 0.05</td>
<td>0.61 ± 0.11</td>
<td>0.58 ± 0.07</td>
</tr>
<tr>
<td>Lung</td>
<td>4.54 ± 0.46</td>
<td>2.44 ± 0.50</td>
<td>1.67 ± 0.24</td>
<td>1.08 ± 0.19</td>
<td>0.88 ± 0.12</td>
</tr>
<tr>
<td>Liver</td>
<td>3.49 ± 0.37</td>
<td>2.20 ± 0.14</td>
<td>1.92 ± 0.23</td>
<td>1.26 ± 0.12</td>
<td>1.28 ± 0.19</td>
</tr>
<tr>
<td>Spleen</td>
<td>5.90 ± 1.36</td>
<td>3.54 ± 0.33</td>
<td>2.44 ± 0.34</td>
<td>1.33 ± 0.09</td>
<td>0.97 ± 0.13</td>
</tr>
<tr>
<td>Pancreas</td>
<td>5.79 ± 0.17</td>
<td>4.06 ± 0.23</td>
<td>4.34 ± 0.20</td>
<td>4.31 ± 0.35</td>
<td>3.51 ± 0.29</td>
</tr>
<tr>
<td>Kidney</td>
<td>6.14 ± 0.43</td>
<td>3.21 ± 0.22</td>
<td>2.76 ± 0.32</td>
<td>2.22 ± 0.28</td>
<td>1.66 ± 0.23</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.01 ± 0.10</td>
<td>0.69 ± 0.08</td>
<td>0.55 ± 0.04</td>
<td>0.35 ± 0.05</td>
<td>0.34 ± 0.03</td>
</tr>
<tr>
<td>Bone</td>
<td>1.71 ± 0.46</td>
<td>1.58 ± 0.30</td>
<td>1.37 ± 0.16</td>
<td>0.97 ± 0.14</td>
<td>0.64 ± 0.15</td>
</tr>
</tbody>
</table>

*Mean ± S.D. (n = 4)

Table 2  Tissue distribution of radioactivity in mice after intravenous injection of $^{11}$C]hexanoate

<table>
<thead>
<tr>
<th>% injected dose/organ*</th>
<th>5 min</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>1.03 ± 0.10</td>
<td>0.60 ± 0.06</td>
<td>0.48 ± 0.03</td>
<td>0.27 ± 0.16</td>
<td>0.16 ± 0.01</td>
</tr>
<tr>
<td>Heart</td>
<td>0.31 ± 0.04</td>
<td>0.21 ± 0.03</td>
<td>0.17 ± 0.02</td>
<td>0.093 ± 0.019</td>
<td>0.077 ± 0.007</td>
</tr>
<tr>
<td>Lung</td>
<td>0.89 ± 0.14</td>
<td>0.51 ± 0.10</td>
<td>0.35 ± 0.07</td>
<td>0.21 ± 0.09</td>
<td>0.17 ± 0.06</td>
</tr>
<tr>
<td>Liver</td>
<td>7.27 ± 1.29</td>
<td>4.27 ± 0.59</td>
<td>3.44 ± 0.35</td>
<td>2.44 ± 0.52</td>
<td>2.66 ± 0.24</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.84 ± 0.11</td>
<td>0.43 ± 0.06</td>
<td>0.33 ± 0.04</td>
<td>0.21 ± 0.08</td>
<td>0.15 ± 0.03</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.99 ± 0.36</td>
<td>0.70 ± 0.10</td>
<td>0.60 ± 0.11</td>
<td>0.61 ± 0.12</td>
<td>0.46 ± 0.19</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.84 ± 0.18</td>
<td>0.55 ± 0.07</td>
<td>0.67 ± 0.23</td>
<td>0.53 ± 0.05</td>
<td>0.43 ± 0.26</td>
</tr>
<tr>
<td>S. Intestine</td>
<td>6.40 ± 0.97</td>
<td>3.22 ± 0.58</td>
<td>2.87 ± 0.65</td>
<td>2.77 ± 0.19</td>
<td>2.83 ± 0.26</td>
</tr>
<tr>
<td>L. Intestine</td>
<td>3.49 ± 0.68</td>
<td>1.97 ± 0.59</td>
<td>1.59 ± 0.85</td>
<td>1.31 ± 0.42</td>
<td>1.10 ± 0.13</td>
</tr>
<tr>
<td>Kidney</td>
<td>3.23 ± 0.25</td>
<td>1.50 ± 0.04</td>
<td>1.45 ± 0.13</td>
<td>1.14 ± 0.19</td>
<td>0.77 ± 0.05</td>
</tr>
<tr>
<td>Testis</td>
<td>0.16 ± 0.02</td>
<td>0.15 ± 0.07</td>
<td>0.12 ± 0.02</td>
<td>0.057 ± 0.011</td>
<td>0.052 ± 0.008</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.13 ± 0.08</td>
<td>0.078 ± 0.060</td>
<td>0.041 ± 0.015</td>
<td>0.057 ± 0.034</td>
<td>0.093 ± 0.050</td>
</tr>
<tr>
<td>Urine</td>
<td>0.76</td>
<td>1.23</td>
<td>1.89</td>
<td>2.86</td>
<td>4.00</td>
</tr>
</tbody>
</table>

*Mean ± S.D. (n = 4)

Table 3  Concentrations of glucose and nonesterified free fatty acids in the plasma of the two groups of mice

<table>
<thead>
<tr>
<th>Glucose (μmol/mL)</th>
<th>12.14 ± 0.86 (14)</th>
<th>6.62 ± 1.14 (28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonesterified free fatty acids (μmol Eq/mL)</td>
<td>1.45 ± 0.40 (28)</td>
<td>1.88 ± 0.43 (28)</td>
</tr>
</tbody>
</table>

Data represent mean ± S.D. (number of mice)

chemical purity greater than 98%.

Tissue distribution of radioactivity after the injection of $^{11}$C]HA into the control mice is summarized in Tables 1 and 2. The level of radioactivity 5 min after the injection was highest in the kidneys, followed by the spleen, pancreas, lungs, liver, brain and heart. The levels in all tissues except for the pancreas decreased rapidly with time. Four % of the total radioactivity was excreted into urine within 90 min after the injection.

Three metabolic radioisotopes, $^{11}$C-HA, $^{3}$H-DG and $^{14}$C-AA, were given simultaneously to the control and fasting mice. After 1 day fasting, plasma glucose significantly decreased to 55% of the control, whereas plasma NEFA increased (Table 3). The time course of radioactivity in the plasma, heart and brain are summarized in Figures 1, 2 and 3. The levels of the three nuclides in the plasma decreased with time (Fig. 1). The fasting delayed the clearance of all three nuclides. In the heart of the fasting mice (Fig. 2), the initial uptake of $^{11}$C-HA was enhanced, and was followed by rapid clearance of the radioactivity as observed in the control, whereas the radioactivity level of $^{14}$C-AA was not affected by the fasting. The uptake of $^{3}$H-DG decreased with time. In the control mice, the initial brain uptake of the $^{11}$C-HA was half of $^{3}$H-DG as high as $^{14}$C-AA (Fig. 3). The $^{11}$C-radioactivity ratios of brain to plasma increased for the first 5 min, remained constant until 30 min and then decreased. Fasting conditions significantly enhanced the brain uptake of all three.
The initial uptake during the first 5 min after the injection of $^{11}$C-HA and $^{14}$C-AA was 1.4–1.5 and 1.3–1.8 times higher than that in the control. The maximal brain uptake of $^3$H-DG at 10 min was 3.4 times higher in the fasting than in the control.

The radiation-absorbed doses are summarized in Table 4. Because of the short half-life of $^{11}$C and the significant amount of expired radioactivity as $^{14}$CO$_2$, radiation-absorbed doses were lower than those of $^{18}$F-labeled compounds.$^{20}$

**DISCUSSION**

This study has indicated the potential of $^{11}$C-HA as a metabolic tracer for PET studies. High uptake and rapid clearance of $^{11}$C-HA were observed in the myocardium, and these were enhanced by fasting. The myocardial uptake of $^3$H-DG in fasting was significantly decreased. This suggests that six carbon-chain HA is degraded by $\beta$-oxidation in the same way as long carbon-chain fatty acids, such as palmitic acid. In the myocardium, there are several groups of enzymes for $\beta$-oxidation, including short-, medium-, long- and very-long-chain acyl-CoA dehydrogenases, that act on straight-chain acyl-CoAs.$^{21}$
The short- and medium-chain acyl-CoA dehydrogenases in the liver and heart act on hexanoyl-CoA.22-24 Deficiency of these enzymes is known.24-26 In the plasma, long-chain fatty acids (C16 and C18) are predominant components, and short-chain fatty acids are minor.25-29 The myocardial extraction of fatty acids containing 12 to 18 carbon atoms tends to decrease with the increase in the number of carbon atoms in the saturated forms.24 In this work, the extraction of 14C-HA by the heart seemed to be lower than that of palmitate, because the heart/blood ratios for 11C-HA were lower than those for 14C-palmitate.4 The level of radioactivity 5 min after the injection of [1-14C]palmitate was 1.6 times higher than that of 14C-HA (unpublished data). The lower uptake of 11C-HA may be explained by the lower affinity of the fatty acid binding protein for the compounds.30-34 In fasting conditions, the blood clearance of 13C-AA was delayed as in case of 11C-HA, although the myocardial uptake and clearance of 14C-AA were not affected.35 Fasting may alter the concentrations of metabolic substrates other than glucose and NEFA in the plasma, as discussed below, and this may affect the blood clearance of 14C-AA.

The brain took up 11C-HA, and the radioactivity gradually disappeared with time. It is known that glucose is the only metabolic fuel in the brain. In the case of extremely abnormal circumstance such as starvation, the major fuel source is shifted from glucose to the ketone bodies, acetoacetate, β-hydroxybutyrate and acetone.34-38 Recently, Hasselbalch et al. confirmed this phenomenon in humans exposed to 3.5 days of starvation, by measuring the glucose metabolism by PET with [18F]fluorodeoxyglucose and the arterio-venous (AV) difference of the several metabolic substrates.39 Although the AV difference in β-hydroxybutyrate was greater in the starvation than in the control, the AV differences in acetocacetate, pyruvate, lactate and free fatty acids were negligible. The mean AV difference for the free fatty acids seems greater, but not significantly, because of individual differences. They did not mention fatty acid utilization in the brain. On the other hand, Oldendorf investigated the brain uptake of short-chain monocarboxylic acids.40 He concluded that the transport of monocarboxylic acids across the blood-brain barrier was mediated by a carrier system. Brain uptake increased with the increase in the number of carbon atoms. The brain uptake of hexanoate, octanoate and decanoate was 76%, 94% and 88%, respectively, of
\(^3\)H-labeled \(\text{H}_2\text{O}\), whereas that of acetate was 14% of \(^3\)H-\(\text{H}_2\text{O}\). We confirmed in this study that the brain uptake of \(^{11}\)C-HA was twice as high as that of \(^{14}\)C-AA. We also confirmed that the brain uptake of \(^{11}\)C-HA at 5 min after injection was ten times that of \([1-{\text{\textsuperscript{14}}}C]\)palmitate (unpublished data). When we considered the previous results for fatty acid metabolism in the brain,\(^{11,16}\) the clearance of \(^{11}\)C-HA from the brain probably indicates that \(^1\)C is washed out as \(^{14}\)CO\(_2\) after the oxidation of \(^{11}\)C-HA. That is, as in the case of \(\beta\)-oxidation in the heart, \(^{11}\)C-HA was metabolized to \(^{13}\)C-acyetyl CoA in the brain, which was further degraded to \(^{14}\)CO\(_2\) via the tricarboxylic acid cycle. This process is the same as the oxidative metabolism of \(^{11}\)C-\(\text{AA}\) in the heart.\(^{34,41,43}\) Otherwise, a part of the \(^{11}\)C-acyetyl CoA is possibly utilized for \textit{de novo} synthesis of amino acids and other compounds,\(^{44,45}\) which was demonstrated for the metabolism of \([1-{\text{\textsuperscript{14}}}C]\)octanoate in the rat brain.\(^4\) It is also considered that \(^{11}\)C-HA could not be incorporated into the lipids, as shown in the metabolism of \([1-{\text{\textsuperscript{14}}}C]\)octanoate.\(^4\) The brain uptake value of \(^{11}\)C-HA (\% injected dose/g tissue) suggests that the \(^{11}\)C-HA is taken up sufficiently to improve its oxidation process by PET. In fasting conditions, the plasma glucose concentration decreased, but the brain uptake of \(^3\)H-DG was enhanced, suggesting that the total uptake of glucose by the brain was preserved. On the other hand, the concentration of NEFA increased and the brain uptake of \(^{11}\)C-HA was enhanced. It is possible that the 1 day fasting enhanced the use of a minor fuel source such as ketone bodies and other substrates. Short-chain fatty acids are minor components in the plasma,\(^{27-29}\) but, \(^{11}\)C-HA may be taken by the brain under low concentrations of glucose in the plasma, via the transport system for \(\beta\)-hydroxybutyrate or monocarboxylic acids discussed above. As another possibility, the delayed clearance of \(^{11}\)C-HA from the plasma resulted in the enhanced uptake. Further studies examining the utilization of \(^{11}\)C-HA in the brain are in progress.

A method for preparing \(^{11}\)C-labeled short-chain fatty acids such as hexanoic is very convenient compared to that for \(^{14}\)C-labeled palmitate. Carboxylation of the Grignard reagents with \(^{14}\)CO\(_2\) is effective, and the reagents are easily removed after hydrolysis by evaporation. The \(^{11}\)C-labeled products are soluble in physiological saline, whereas serum albumin or detergent is required to solubilize \(^{11}\)C-palmitate. An improved method with ion-exchange resin instead of ether extraction, which is suitable for routine production of short-chain fatty acids including \(^{11}\)C-acetate, will be described elsewhere.

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\section*{References}


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44. Badar-Goffer RS, Bachelar HS, Morris PG. Cerebral metabolism of acetate and glucose studied by 13C-n.m.r. spectroscopy. *Biochem J* 266: 133–139, 1990.