BIOIMAGING IN NEURODEGENERATION
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EDITED BY

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Preface

Bioimaging is in the forefront of medicine for the diagnosis and treatment of neurodegenerative disease. Conventional magnetic resonance imaging (MRI) uses interactive external magnetic fields and resonant frequencies of protons from water molecules. However, newer sequences, such as magnetization-prepared rapid acquisition gradient echo (MPRAGE), are able to seek higher levels of anatomic resolution by allowing more rapid temporal imaging. Magnetic resonance spectroscopy (MRS) images metabolic changes, enabling underlying pathophysiologic dysfunction in neurodegeneration to be deciphered. Neurochemicals visible with proton ¹H MRS include N-acetyl aspartate (NAA), creatine/phosphocreatine (Cr), and choline (Cho); NAA is considered to act as an in vivo marker for neuronal loss and/or neuronal dysfunction. By extending imaging to the study of elements such as iron—elevated in several neurodegenerative diseases—laser microprobe studies have become extremely useful, followed by X-ray absorption fine-structure experiments.

Positron emission tomography (PET) and single-photon emission tomography (SPECT) have become important tools in the differential diagnosis of neurodegenerative diseases by allowing imaging of metabolism and cerebral blood flow. PET studies of cerebral glucose metabolism use the glucose analog [¹⁸F]fluorodeoxyglucose (FDG) and radioactive water (H₂¹⁵O) and SPECT tracers use ⁹⁹mTc-hexamethylpropylene amine oxime (HMPAO), and ⁹⁹mTc-ethylcysteinyl dimer (⁹⁹mTc-ECD). Moreover, direct imaging of the nigrostriatal pathway with ⁶-⁹⁹mTc-FCWAY helps to predict the progression of AD via mild cognitive impairment (MCI) studies.

Novel neuroimaging technologies, such as neuromolecular imaging (NMI) with a series of newly developed BRODERICK® sensors, directly image neurotransmitters, precursors, and metabolites in vivo, in real time and within seconds, at separate and selective waveform potentials. NMI, which uses an electrochemical basis for detection, enables the differentiation of neurodegenerative diseases in patients who present with mesial versus neocortical temporal lobe epilepsy. In fact, NMI has some remarkable similarities to MRI insofar as there is technological dependence on electron and proton transfer, respectively, and further dependence is seen in both NMI and MRI on tissue composition such as lipids. NMI has already been joined with electrophysiological (EEG) and electromyographic (EMG) studies to enhance detection capabilities; the integration of NMI with MRI, PET, and SPECT can be envisioned as the next advance.

The tracer molecule, [¹¹C]α-methyl-L-tryptophan (AMT) is already used with PET to study serotonin (5-HT) deficiencies, presumably attributable to kynurenine enhancement in neocortical epilepsy patients. Moreover, AMT PET, in addition to FDG PET, provides reliable diagnosis for pediatric epilepsy syndromes such as West’s syndrome. Important in children with cortical dysplasia (CD), FDG PET delineates areas of altered glucose, which can be missed by MRI. The new tracer, [¹¹C]fluoromazenil used with PET (FMZ PET), has found utility in the detection of epileptic foci in CD patients with partial epilepsies, and yet normal structural imaging is observed. Another new 5-HT₁A tracer for PET imaging in abnormal dysplastic tissue is a carboxamide compound called [¹⁸F]FCWAY.

Diagnosis of neocortical epilepsy has been significantly advanced by IOS or intrinsic optical signal imaging. IOS has its basis in the light absorption properties of electrophysiologically active neural tissue, activity caused by focal alterations in blood flow, oxygenation of hemoglobin, and scattering of light. IOS can map interictal spikes, onsets and offsets, and horizontal propagation lines. Thus, IOS is useful for diagnosing “spreading epileptiform depression.” As with NMI, IOS holds promise for intraoperative cortical mapping wherein ictal and interictal margins can be more clearly defined. As does intraoperative MRI (iMRI) with neuronavigation, these technologies provide what is called “guided neurosurgery.” Correlative imaging of general inhalational anesthetics such as nitrous oxide (N₂O) during intraoperative surgery is made possible by NMI technologies with nano- and microsensors.
NMI and MRI also enable the differential detection of white matter versus gray matter in discrete neuroanatomic substrates in brain, detection which is critical to both the epilepsies and the leukodystrophies. Although NMI is in its early stage in this arena, the immediate and distinct waveforms that distinguish white from gray matter are impressive. Moreover, the early finding of a leukodystrophy by MRI, particularly relevant for metachromatic leukodystrophy (MLD), Krabbe’s disease (KD), and X-linked adrenoleukodystrophy (ALD), allows clinicians therapeutic interventions before overt symptoms are exhibited. Imaging technologies, pathologies, clinical features, and treatments for these and other leukodystrophies, including peroxisomal disorders and leukodystrophies with macrocrania (Canavan’s disease and Alexander’s disease), are presented here in precise detail. The van der Knaap syndrome is a recently described leukodystrophy in vacuolating megalencephalic leukoencephalopathy (VMI). This vanishing white matter disease highlights the potential of MRS imaging, which was used in its identification.

Bioimaging in Neurodegeneration provides extensive detail on pediatric mitochondrial disease, including imaging, pathologies, clinical features, and treatment or lack of treatment. It is extremely important to note that in pediatric mitochondrial cytopathies, a frequent finding on MRI is abnormal myelination, and infants with leukoencephalopathies, especially leukodystrophies, should be evaluated for mitochondrial cytopathy. Infarct-like, often transient lesions not confined to vascular territories are the imaging hallmark of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). $^{31}$P MRS, which can measure transient changes in nonoxidative adenosine triphosphate (ATP) synthesis, and $^{1}$H MRS, which can measure lactate, are included in the mitochondrial imaging technologies.

Thus, Bioimaging in Neurodegeneration fulfills the current need to bring together neurodegeneration with bio- and neuroimaging technologies that actually enable diagnosis and treatment. Professionals in neurology, psychiatry, pharmacology, radiology, and surgery are among many who will greatly benefit. Neurodegenerative disease is divided into four areas, i.e., Parkinson’s disease, Alzheimer’s disease, the epilepsies, and the leukodystrophies. Chapter authors were selected for their formidable expertise in each field of medicine, their expertise in imaging technologies, and their scholarly contributions to medicine and science. Our appreciation is extended to them, and their staffs, for their fine research. We thank the editors and staff at Humana Press for their excellent assistance and support.

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**CHAPTER 2**  Figs. 1–5

**CHAPTER 3**  Fig. 2

**CHAPTER 5**  Figs. 1, 4

**CHAPTER 7**  Fig. 1

**CHAPTER 10**  Figs. 2, 3, and 6

**CHAPTER 11**  Fig. 1

**CHAPTER 14**  Figs. 1, 3, 6, 8, 9, 11–17

**CHAPTER 15**  Figs. 1–5, 11

**CHAPTER 16**  Figs. 2–5
Prologue

Nano- and Microimaging Surgical Anesthesia in Epilepsy Patients

PATRICIA A. BRODERICK, PhD, DAVID N. RAHNI, PhD, AND STEVEN V. PACIA, MD

Nitrous oxide (N₂O) is a simple and small molecule, consisting of two nitrogen atoms and one oxygen atom (Fig. 1). Yet, its anesthetic, analgesic, and psychotropic properties are indisputable (1–3). Nitrous oxide is reported to act via opiate mechanisms because it induces met-enkephalin and β-endorphin release in rat and human, and the antinociceptive properties of nitrous oxide are reversible by naloxone (4,5). Also, but likely not exclusively, nitrous oxide may exert its effects via glutamate receptors, that is, administration of (80%) nitrous oxide to rat hippocampus depresses excitatory currents evoked by N-methyl-D-aspartate (6,7).

The combination of nitrous oxide and oxygen has found its way into prehospital emergency treatment of pain (2). Under the proprietary names, Entonos® and Dolonox®, this combination in a 40–60% ratio is used by paramedics when treating acute myocardial infarction (8). In some areas of the world, it is used in emergency medicine in lieu of opioid analgesics for the management of painful injuries (9).

In the hospital setting, intraoperatively nitrous oxide is used adjunctly with other general anesthetics for its well-known “second gas effect,” a phenomenon that is caused by its ability to diffuse quickly from alveoli. However, nitrous oxide, even in combination with oxygen, rarely is used alone in surgery because it is a relatively weak general anesthetic (low blood/gas solubility partition coefficient).

Interestingly, in studies used to map the effects of analgesics on pain, cerebral substrates for the nociceptive effects of nitrous oxide have been identified. Using low concentrations (20%) nitrous oxide was imaged using positron emission tomography and cerebral blood flow (rCBF). Inhalation of 20% nitrous oxide was found to be associated with enhanced rCBF in the anterior cingulate cortex (area 24), decreased rCBF in the hippocampus, posterior cingulate (areas 23, 24), and decreased rCBF in the secondary visual cortices (areas 18, 19; ref. 10).

Despite the importance of this small and simple molecule in surgery, emergency medicine, and dentistry alone, there are virtually little or no direct techniques available to detect nitrous oxide unchanged in living tissue. Our purpose here is to present such a technique using neuromolecular imaging (NMI) and carbon based nano- and microsensors.

We describe the experimental design for and the results from in vitro assays, i.e., studies of nitrous oxide as N₂O is diffused into an electrochemical cell as well as those from in vivo assays, i.e., studies of nitrous oxide which has stabilized in living tissue from N₂O infusion.

This is the first report of the experimental assay for the gaseous solution, nitrous oxide and the results from such, in vitro. High purity (99.9%) commercially available nitrous oxide (T.W. Smith, Brooklyn, NY) was diffused using a flowmeter, calibrated at 10 psi, into an electrochemical cell containing saline/phosphate buffer for 5 min to allow the gas to reach saturation at room temperature. The flowmeter was purchased from Fisher Scientific (Bridgewater, NJ). Nitrous oxide concentrations in the approximate range of 10–100 μM were achieved. Figure 2 shows a representative recording of nitrous oxide detection in vitro. Nitrous oxide detection occurred at the oxidation (half-wave) potential of 0.53 ± 0.02 V. In addition, DA and 5-HT signals are shown because increasing concentrations of DA and 5-HT were aliquoted into the electrochemical cell for use as standards. Thus, studies with the monoamines were conducted, which show the selective detection of nitrous oxide in the presence of the monoamine neurotransmitter.

Procedures for the detection of neurotransmitters and neurochemicals by BRODERICK PROBE® sensors are described (11–20).

This is also the first report of the experimental assay for the gaseous solution, nitrous oxide, and the results from such, in vivo. Resected living tissue (hippocampal and neocortical) from temporal lobe epilepsy (TLE) patients was studied. Methods for patient classification and methods for delineating neurochemical profiles are previously published. Patients were administered nitrous oxide-oxygen anesthesia in a 40/60% concentration during intraoperative surgery. Figure 3 shows a representative recording from an NTLE patient, in vivo. These images from TLE patients show reliable nitrous oxide signals that occurred at the oxidation (half-wave) potential of 0.53 ±
0.02 V, which is consistent with the detection of nitrous oxide at the same oxidation potential in vitro. Further evidence for the reliable detection of nitrous oxide comes from studies in this laboratory which has shown the separate detection of nitric oxide (NO) at an approximate oxidation potential of 0.75 V (21). These data are in general agreement with detection of NO using the carbon fiber electrode (22). Moreover, the reliable detection of nitrous oxide comes from the known predictive ability to detect oxygen at early negative potentials, again separating the detection of oxygen from that of nitrous oxide. Finally, the stability of nitrous oxide at physiological temperatures is known (url: www.chm.bris.ac.uk/motm/n2o/n2oh.htm [23; retrieved on or about June 3, 2004]). Thus, these studies confirm the selective detection of nitrous oxide in the absence and presence of the monoamine neurotransmitters.

Table 1 shows the neuroanatomic location of nitrous oxide signals imaged in distinct neocortical neuroanatomic structures and hippocampal subparcellations. As expected, there was no
Table 1
Nitrous Oxide (N\textsubscript{2}O) in Resected Temporal Tissues From Human Epilepsy Patients

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Epilepsy Type</th>
<th>N\textsubscript{2}O Signals Imaged in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>MTLE Neocortex (G)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NTLE Neocortex (G,W); HPC (Granular cells)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NTLE Neocortex (G,W); HPC (Polymorphic layer)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>MTLE Neocortex (G)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>MTLE HPC (Subiculum)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>MTLE HPC (Pyramidal layer)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>NTLE HPC (Pyramidal layer)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>NTLE Neocortex (G)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>MTLE Neocortex (G,W); HPC (Polymorphic, Pyramidal, Mol. layers)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>MTLE Neocortex (G); HPC (Subiculum)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>MTLE Neocortex (G,W); HPC (Polymorphic layer)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>MTLE Neocortex (G,W)</td>
<td></td>
</tr>
</tbody>
</table>

G is gray matter; W is white matter; Patients 7, 11, and 12: MTLE did not exhibit N\textsubscript{2}O; NTLE, neocortical temporal lobe epilepsy; MTLE, mesial temporal lobe epilepsy.

apparent difference in the degree of nitrous oxide imaging between NTLE and MTLE patients, given the caveat that there were more MTLE patients than NTLE patients.

In summary, the significance of imaging nitrous oxide anesthesia in living tissue is paramount in neurology, neurosurgery, emergency medicine, toxicology, substance abuse (see ref. 24 for a recent review), and dentistry. Moreover, the BRODERICK PROBE\textsuperscript{®} sensors image nitrous oxide signals on line yet separately from monoamines, metabolites, precursors. These data provide promise for optimizing such a technology for selective nano- and micro-monitoring and measuring nitrous oxide intraoperatively.

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