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Functional Brain Imaging Using PET

by:

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FUNCTIONAL BRAIN IMAGING USING PET

STATEMENT OF OBJECTIVES

The purpose of this correspondence lesson is to introduce the reader to current applications of neuroimaging using the technology of positron emission tomography.

Upon successful completion of this material, the reader should be able to:

1. Discuss the principles of positron emission tomography (PET).
2. Cite advantages and limitations of PET compared to other neuroimaging techniques.
3. Discuss PET radiopharmaceuticals used for functional brain imaging.
4. Describe PET methodologicss for assessment of physiological parameters of brain function.
5. List indications for clinical PET imaging of the brain to evaluate patient status.
6. Discuss the role of PET in the evaluation of cerebrovascular disease.
7. Explain procedures for PET activation studies for investigation of human cognition.
8. Discuss applications of PET imaging of movement disorders.
9. Present examples of the use of PET for evaluation of psychiatric conditions.
10. Discuss applications of PET for the evaluation of centrally-active drugs in vivo.

Editor’s note: A review of neuroanatomy may assist the reader’s understanding of the material contained in this lesson.
INTRODUCTION

There is keen interest in the application of imaging techniques to better understand brain physiology and pathophysiology. Potential applications of these techniques are for diagnosis and staging of disease, as well as monitoring therapeutic interventions. Positron emission tomography (PET) is a specialized form of nuclear medicine that offers distinct advantages over alternative methods for imaging the brain. Unlike computerized tomography (CT) or magnetic resonance imaging (MRI), which visualize brain anatomy, PET acquires image data of cerebral physiology. This is because PET information is derived from the tissue distribution of positron-emitting drugs, which is determined by the specific metabolic and biochemical processes that affect the radiopharmaceutical in vivo.

PET also has advantages compared to conventional nuclear medicine imaging of the brain. Radiopharmaceuticals that are impossible to prepare with gamma-emitting radionuclides can be synthesized with the positron-emitting radionuclides commonly employed for PET. Furthermore, PET instrumentation has greater sensitivity and superior image resolution compared to planar imaging devices. PET images can be accurately corrected for tissue attenuation, so radiopharmaceutical localization can be quantified using tracer kinetic models. These characteristics make positron emission tomography a unique methodology for the noninvasive assessment of brain function in health and disease.

This continuing education lesson will review the commonly-used PET radiopharmaceuticals and methodologies applied for measurement of physiological brain parameters. The use of these techniques for the study of common neurological disorders will be discussed, and the employment of PET for in vivo evaluation of centrally-acting drugs will be described. The course is anticipated to give the participant insight into the use of PET for functional brain imaging, as well as an appreciation of the great potential of this powerful imaging technique for improving our understanding of cerebral physiology, pathophysiology, and neuropharmacology.
PRINCIPLES OF PET IMAGING

PET imaging intrinsically depends on the physics of positron decay. When proton-rich nuclei decay by emission of a positron, the emitted particle interacts with an orbital electron to create annihilation radiation. The annihilation radiation is comprised of two 511-keV gamma rays emitted at approximately 180 degrees from one another. Due to the colinearity of these gamma rays, coincidence circuits can be designed in which an orbital electron to create annihilation radiation. The two detectors only if the 511-keV gamma ray is detected simultaneously in both detectors. Assembly of rings of such coincidence circuits serves as the framework of PET scanners, in which “electronic collimation” of emitted radiation is provided through the coincidence requirement. Reconstruction algorithms are used to derive PET images from the multiple coincidence lines of the various coincidence circuits.

Compared to alternative modalities for imaging the brain, PET has certain limitations. Because PET requires the synthesis of radioactive drugs, it is a more expensive technique than methods like MRI or CT. Imaging procedures also tend to be more complicated for PET, since they usually involve analysis of blood samples. In addition, PET has an image resolution (2-3 mm limit) that is poorer than either MRI or CT. Despite these limitations, there is a major factor that drives the expanding use of PET for imaging applications. This is that PET is virtually the only noninvasive means for acquisition of functional, as opposed to anatomical, information about the living brain. It is this singular characteristic that ensures that PET will continue to be a valuable means for investigation of cerebral physiology, and the manner in which it changes in response to disease or drug action.

PET RADIOPHARMACEUTICALS

Because PET detects the distribution of radioactivity in the brain following the injection of a radioactive drug, the utility of the technique is circumscribed by the radiotracers that are available for imaging studies. The radionuclides used for labeling PET tracers are generally created with use of an in-house medical cyclotron. The physical half-lives of these radionuclides range from 2 minutes for oxygen-15 to 110 minutes for fluorine-18. The short half-life of oxygen-15 labeled drugs facilitates repeat PET studies within the same imaging session, whereas the longer-lived carbon-11 or fluorine-18 labels are convenient for more lengthy imaging procedures. The radiopharmaceuticals used for PET studies must meet stringent requirements for drug purity, and must be prepared in useful radiochemical yield within the constraints imposed by the half-life of the relevant isotope. The radiopharmaceuticals that meet these requirements, and are employed for neuro-PET studies, are listed in Tables 1 and 2.

Table 1 describes tracers that are used for measurement of cerebrovascular or metabolic parameters of brain function. These include oxygen-15 labeled water and carbon monoxide. [15O]water is used for measurement of cerebral perfusion, whereas [14C]carbon monoxide is used for determination of regional cerebral blood volume. The short half-life of these tracers (2 minutes) is well-suited for serial studies within the same imaging session, or as ancillary measurements with studies using longer-lived radiopharmaceuticals.

[18F]Fluorodeoxyglucose (18F]FDG) is a very popular PET tracer used for measurement of cerebral glucose utilization. The 2-hour half-life and efficient radiosynthesis of this radiopharmaceutical facilitate its preparation in multi-dose batches for subsequent dispensing into individual subject dosages.

An additional PET tracer that is labeled with fluorine-18 is [18F]flurorodopa ([18F]FD). This radiopharmaceutical is used to measure neuronal decarboxylase activity, which can be used to estimate the number of dopamine neurons within the brain. Unlike [18F]FDG, [18F]FD is prepared on a unit-dose basis (one synthesis per study subject) due to the lower production yields.

Another category of radiopharmaceutical used for PET study of cerebral metabolism includes the radiolabeled amino acids. These are generally labeled with the 20-minute half-lived carbon-11, and are prepared on a unit-dose basis. Many different amino acids have been employed for this purpose, and although [14C]leucine and [14C]methionine have been most extensively investigated, there is no clear consensus as to the optimum agent for use in neuro-PET.

Table 2 lists the multitude of receptor-binding PET radiopharmaceuticals that have been used in human studies. Receptor-binding radiotracers have special requirements. The radioligands must be prepared in high specific activity to avoid saturation of binding sites or induction of pharmacological and toxicological side effects. These complicated molecular structures require relatively lengthy preparation methods, and are labeled with either carbon-11 or fluorine-18. Although carbon-11 is more commonly used as a radiolabel, fluorine-18 is preferred as a label for tracer kinetics that require longer imaging sessions. As shown in the table, radiopharmaceuticals exist for PET study of dopamine, serotonin, benzodiazepine, opiate, and muscarinic cholinergic receptors of the brain. The cerebral dopaminergic receptor system has been the most intensively investigated, and carbon-11 and fluorine-18 labeled radiopharmaceuticals are available for imaging D1 and D2 subtypes. With the exception of [18F]falanescin, which is used for measurement of serotonin-2a receptor binding, the remaining radioligands commonly used for neuro-PET imaging are labeled with the 20-minute half-lived carbon-11.

PET METHODOLOGY

A major strength of PET imaging is its capability for quantifying the tissue accumulation of radioactivity.
Table 1. PET Radiopharmaceuticals for Imaging Cerebral Metabolism

<table>
<thead>
<tr>
<th>Drug</th>
<th>$T_{1/2}$ (min)</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[^{15}O]$Water</td>
<td>2</td>
<td>Regional cerebral blood flow</td>
</tr>
<tr>
<td>$[^{15}O]$Carbon monoxide</td>
<td>2</td>
<td>Regional cerebral blood volume</td>
</tr>
<tr>
<td>$[^{11}C]$Amino acids (various)</td>
<td>20</td>
<td>Amino acid utilization</td>
</tr>
<tr>
<td>$[^{18}F]$Fludeoxyglucose</td>
<td>110</td>
<td>Glucose utilization</td>
</tr>
<tr>
<td>$[^{18}F]$Fluorodopa</td>
<td>110</td>
<td>Decarboxylase activity</td>
</tr>
</tbody>
</table>

Table 2. Selected Receptor-Binding PET Radiopharmaceuticals

<table>
<thead>
<tr>
<th>Receptor</th>
<th>$[^{11}C]$-Labeled Ligands</th>
<th>$[^{18}F]$-Labeled Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine D2</td>
<td>$[^{11}C]$Raclopride</td>
<td>$[^{18}F]$(N-Methyl)benperidol</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]$(N-Methyl)spiperone</td>
<td>$[^{18}F]$(N-Fluoroethyl)spiperone</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]$(N-Methyl)spiperone</td>
<td>$[^{18}F]$(N-methyl)spiperone</td>
</tr>
<tr>
<td>Dopamine D1</td>
<td>$[^{11}C]$SCH 23390</td>
<td>$[^{18}F]$Altanserin</td>
</tr>
<tr>
<td>Serotonin S2</td>
<td>$[^{11}C]$(N-Methyl)ketanserin</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>$[^{11}C]$Flumazenil</td>
<td></td>
</tr>
<tr>
<td>Opiate</td>
<td>$[^{11}C]$Carfentanil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]$Diprenorphine</td>
<td></td>
</tr>
<tr>
<td>Muscarinic</td>
<td>$[^{11}C]$(N-Methyl)-4-piperidyl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>benzylate</td>
<td></td>
</tr>
</tbody>
</table>
Unlike qualitative imaging, in which the relative count density within the field of view is detected, quantitative PET imaging facilitates the acquisition of the data necessary for tracer kinetic modeling of brain images and derivation of physiological parameters. For tracer kinetic modeling, two types of data are acquired during the imaging session. These are broadly categorized as image data and peripheral blood data. Using the PET scanner, the tissue accumulation of radioactivity is acquired as a function of time on a regional basis. This image data is compared to measurements made on blood samples removed from the subject in a serial manner. Blood samples can be analyzed for tracer concentration, radiometabolites, or protein binding, depending on the specific requirements of the tracer kinetic model that is employed.

To accomplish quantitative PET of the brain, certain features are necessary in the imaging protocol. These include a transmission scan to correct for tissue attenuation, cross-calibration of the radiation detection efficiency of the scanner with an external radiation detector, and assessment of scanner uniformity using a phantom source of radioactivity. These measurements are needed to assure that imaging artifacts are absent, and to assure that PET counts can be accurately compared to activity measured in peripheral blood samples. Once these calibration measurements have been made for the instrumentation, the system can then be employed for parameter estimation methods.

An extremely useful parameter of brain function that can be measured by PET is regional cerebral blood flow (rCBF). The rCBF is used in activation studies to determine brain tissues that are called into play during certain mental processes, and to assess deficits or changes in brain blood flow that accompany pathological processes. The principle behind cerebral perfusion measurements is that tracer accumulation within a region of interest is directly proportional to the rate of delivery of a freely-diffusible tracer to that region. The rCBF is calculated from the tissue accumulation of activity (measured by PET) and the input function (measured in blood samples removed from an arterial line). The freely-diffusible tracer that is used is [15O]water, delivered either as a bolus injection, or as inhaled [15O]carbon dioxide which is converted in the blood into [15O]water. The first methodological technique is referred to as the autoradiographic method, whereas the second is called the equilibrium method.

Another cerebrovascular parameter that is measured by PET is regional cerebral blood volume (rCBV). This measurement is important in cerebrovascular disease, because changes in cerebral blood volume reflect the vasodilation that accompanies decreased perfusion pressure. It is also used as an adjunct measurement in studies involving other PET tracers, since accurate measurement of tracer accumulation within tissue requires a correction for the amount of activity located within the intravascular space of the brain. The rCBV is measured using [15O]carbon monoxide as a radiopharmaceutical. After the radioactive gas is inhaled, it forms [15O]carboxyhemoglobin, which remains confined to the plasma space. The rCBV is calculated from the ratio of the tissue radioactivity concentration (measured by PET) to the radioactivity measured in a sample of peripheral blood. The simple dilution principle used in this calculation includes a correction for the difference between cerebral hematocrit and large-vessel, peripheral hematocrit.

A metabolic parameter that is altered by various brain pathologies is the regional cerebral rate of oxygen utilization (rCMRO2). This parameter is determined using PET methodology, although complicated protocols are required due to the in vivo behavior of [15O]oxygen. Typically, about 40% of plasma [15O]oxygen is extracted by brain tissue, where it is metabolically converted to [15O]water, which then clears from the brain. The protocol for PET determination of rCMRO2 thus requires PET measurement of the oxygen extraction ratio (OER) of inhaled [15O]oxygen, together with determination of the input function by measurement of the radioactivity content in arterial blood samples. In addition to this, measurement of rCBF with [15O]water is needed to determine delivery of the tracer to brain regions, and to correct for the recirculating [15O]water of metabolism. Also, measurement of rCBV with [15O]carbon monoxide is required to correct for the approximately 60% of [15O]oxygen that is not extracted by tissue, but instead remains in the extravascular space. From all of this data, the CMRO2 is calculated as the product of CBF, OER and the arterial oxygen content.

Another metabolic measurement that is made in neuro-PET studies is the regional cerebral rate of glucose utilization (rCMRG). This parameter is measured using fluorine-18 Fluorodeoxyglucose ([18F]FDG). [18F]FDG is transported across the blood-brain barrier by the same transport system as glucose, and is phosphorylated in tissue, like glucose, by hexokinase to form [18F]FDG-6-phosphate. Unlike glucose, [18F]FDG-6-PO4 does not undergo further metabolism, but instead remains "metabolically trapped" at the site, facilitating the calculation of rCMRG from the local tissue radioactivity. A three-compartment model is used to describe the behavior of [18F]FDG, and an operational equation has been developed that describes the rCMRG in terms that are measured in the PET protocol. These measurements are the regional tissue activity at a single time point, the arterial plasma concentration of [18F]FDG over time, and the plasma glucose concentration. These data are acquired by imaging the subject at about 45 minutes after radiopharmaceutical injection, and serial collection of blood samples for measurement of the concentration of [18F]FDG and glucose. The equation also contains rate constants and a lumped constant, which corrects for differences between FDG and glucose transport.
and phosphorylation. In the operational equation, standard population averages are used for these constants.

Aside from the above PET techniques for routine measurement of cerebrovascular and metabolic parameters of the brain, there also exist other methodologies that assess more specialized aspects of brain physiology. These methods are less universally applied, either because their application is less general, or because there are multiple tracer kinetic models available, with no clear consensus on which one is optimum. Examples of these techniques are models for estimating neurotransmitter synthesis, together with analysis of peripheral blood samples and correction for rCBF and rCBV.9

**CLINICAL PET**

An important issue in health care is the delivery of cost-efficient services that improve patient outcomes. PET is sometimes used in the clinical setting for this purpose,10 and such “clinical PET” has applications that are specific to neurological function.

There are certain regulatory and reimbursement issues that set clinical PET apart from PET that is employed strictly for research studies. Whereas research PET projects are limited to small numbers of subjects to answer a scientific hypothesis, clinical PET is applied to unlimited numbers of patients as a routine health care service. Research projects are funded through competitive grants, whereas clinical PET studies are reimbursed by third-party payers.

While research PET may be used to evaluate a novel tracer or a new PET methodology, clinical PET is limited to the use of established PET techniques for specific indications. In clinical PET, both tracer and imaging procedure have already been validated to be effective in disease diagnosis. Production procedures for tracers used in research projects are generally approved by institutional Radioactive Drug Research Committees. In contrast, radioactive drug production for clinical PET follows procedures described in an IND or NDA granted by the FDA, or is compounded under the order of a nuclear medicine physician.

Several neuro-PET applications have indications for use as clinical PET procedures. Two commonly used procedures are the application of $[^{18}F]$FDG for evaluation of brain tumors, and the use of $[^{18}F]$FDG for examination of epilepsy (Table 3). Both procedures employ $[^{18}F]$FDG, a radiopharmaceutical with well-established production and quality control criteria, with PET methodologies that have been validated in multi-site studies.

The use of $[^{18}F]$FDG for brain oncology studies by PET is based on the fact that many brain tumors grow rapidly, and hence have an elevated CMRG. Tumors thus appear as a hot spot on PET scans. $[^{18}F]$FDG/PET is used clinically to stage tumor malignancy and to distinguish recurrent tumor from radiation necrosis.

The staging of brain tumors is one of the applications of clinical PET.12 The advantages of $[^{18}F]$FDG/PET for this application are that it is more predictive of tumor aggressiveness than CT or MRI, it demonstrates metabolically active areas and growth direction, and it differentiates active tumor from edematous regions of the brain. PET imaging is also less invasive than histological grading, and often increases test sensitivity when combined with histological results. A disadvantage of $[^{18}F]$FDG as a tumor marker for PET is that CMRG is highly structured in brain tissue, so that tumor/background contrast is low in medium- or low-grade tumors.13 The low image contrast makes the delineation of these types of tumors difficult. This is unfortunate, because early intervention in such tumors might be anticipated to have beneficial effects for the patient. This limitation has led investigators to examine
Table 3. Selected Clinical Indications for Neuro-PET

<table>
<thead>
<tr>
<th>Condition</th>
<th>Radiopharmaceutical</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>[^{18}\text{F}]\text{FDG}\text{glucose}</td>
<td>Identification of site of epileptic foci</td>
</tr>
<tr>
<td>Cancer</td>
<td>[^{18}\text{F}]\text{FDG}\text{glucose}</td>
<td>Distinguish radiation necrosis from recurrent tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Identification of size and extent of tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Determination of direction of tumor growth</td>
</tr>
</tbody>
</table>

alternative approaches, notably amino acid utilization, as potential PET methodologies for brain oncology studies.

Many brain tumors are inoperable, and are treated by radiation therapy with an external beam source. A complication of this treatment is radiation necrosis, and treatment failure results in tumor regression following therapy. CT or MRI is unable to distinguish between tumor and scar tissue, since both appear as an image defect. Because \[^{18}\text{F}]\text{FDG}\text{ selectively accumulates in growing tissue, and not in scar tissue, the distinction between the two is readily apparent in PET scans.}\[11]

Another major clinical PET application is the use of \[^{18}\text{F}]\text{FDG}/\text{PET}\text{ for examination of epilepsy. To date, this is the only FDA-approved indication for }[^{18}\text{F}]\text{FDG. Approximately 50% of epileptics are unresponsive to drug therapy, and may benefit from surgery if the location of the focal site is known. Structural abnormalities are rarely detected in epileptics using CT or MRI, so epileptic sites cannot be detected in this manner. Noninvasive EEG measurements using scalp electrodes are useful only for foci located at the cortical surface. For foci located deep within the brain, an invasive surgical procedure with implanted depth electrodes is used. Thus, identification of these sites is invasive, expensive and involves substantial patient discomfort.}

[^{18}\text{F}]\text{FDG}/\text{PET}\text{ is a noninvasive methodology that identifies epileptic foci regardless of location within the brain.}\[14] CMRG within the focus is increased during the ictal phase, and decreased during the interictal phase. Scanning the patient during the seizure-free phase will thus visualize a cold spot in the PET image at the site of the focus. \[^{18}\text{F}]\text{FDG}/\text{PET}\text{ scanning of epileptics is generally done in conjunction with EEG, to increase the sensitivity of selecting patients for surgical exploration.}

CEREBROVASCULAR DISEASE

Ischemia can be defined as a condition in which tissue perfusion is inadequate to meet energy requirements. If sufficiently severe, ischemia can lead to stroke, which is associated with irreversible loss of the functional and structural integrity of brain tissue. The biochemical sequela of ischemia are complicated, and better understanding of the cascade of events that takes place may improve management of this condition.

PET, with its ability to identify biochemical changes that precede structural alterations, is well-suited to study the progression from the reversible effects of ischemia to the irreversible changes that occur with stroke and brain infarction. The lesions that are detected by PET precede those visualized by MRI or CT, and involve larger tissue regions. PET has been successfully used to stage disease severity, as well as to monitor interventional therapies and to direct clinical decision making.

The physiological events that take place in stroke are an initial, severe decrease in perfusion, followed by variable recovery of blood flow over time and development of neuronal damage.\[15] PET is used to examine primary hemodynamic changes, as well as the secondary metabolic derangements that occur (Table 4). Hemodynamic measurements are made with use of \[^{15}\text{O}]\text{water}\text{ and }[^{15}\text{O}]\text{carbon monoxide}, while metabolic measurements are made using \[^{18}\text{O}]\text{oxygen}. \[^{18}\text{F}]\text{FDG}\text{ is not indicated for examination of infarction, because localization in ischemic tissue sometimes shows a contradictory increase. The increase in CMRG is secondary to the induction of anaerobic glycolysis in the poorly-perfused region.}

Table 4. Cerebrovascular Conditions Studied with PET

<table>
<thead>
<tr>
<th>Condition</th>
<th>Radiopharmaceutical</th>
<th>Image Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia</td>
<td>[^{15}\text{O}]\text{Water}\text{ or }[^{15}\text{O}]\text{Oxygen}</td>
<td>Decreased rCBF, Increased rOER</td>
</tr>
<tr>
<td>Infarction</td>
<td>[^{15}\text{O}]\text{Water}\text{ or }[^{15}\text{O}]\text{Oxygen}</td>
<td>Decreased rCBF, Increased rOER</td>
</tr>
<tr>
<td>TIA</td>
<td>[^{15}\text{O}]\text{Water}, [^{15}\text{O}]\text{Carbon monoxide}</td>
<td>Decreased CBP/CBV ratio</td>
</tr>
</tbody>
</table>

Hemodynamic changes are measured directly by PET as rCBF, whereas metabolic changes are usually measured as CMRO\text{2}. These two physiological parameters are related to one another via the oxygen extraction ratio (OER).

\[
\text{CMRO}_2 = \text{CBF} \times \text{arterial O}_2 \times \text{OER}
\]
Oxygen-15 PET studies show that the healthy brain has "perfusion reserve," in which the rCBF decreases without a catastrophic drop in CMRO₂, since the OER of the brain increases (16). In ischemia, the deceased rCBF is compensated for by an increase in the OER. Unfortunately, perfusion reserve is ultimately limited, and for substantial decreases in CBF, the OER reaches a maximum that only partially compensates for flow loss. The rCMRO₂ therefore decreases, metabolic damage to neurons occurs, and the irreversible changes of stroke develop. The transition from reversible ischemia to infarction is thus most closely monitored via PET as a fall in the OER of the brain.

Oxygen-15 PET studies have identified that for rCBF less than 10 mL/100g/min, brain tissue is infarcted, whereas for flows above approximately 18 mL/100g/min, tissue is generally ischemic. The critical zone is the "ischemic penumbra," in which tissue has intermediate perfusion rates, and can either revert to ischemia or progress to infarct with irreversible damage. Limitations of PET methodology in examining the ischemic penumbra are that the instrument resolution is often too coarse to identify the affected zones, and there is also the complicating effect of reperfusion. It is for this reason that PET evaluation of stroke requires metabolic measurements (CMRO₂ or OER) using [¹⁵O]oxygen, as well as perfusion measurements using [¹⁵O]water.

The perfusion defect in ischemic brain can be categorized as misery perfusion or luxury perfusion. Misery perfusion refers to the condition in which the CBF is less than the tissue demand, and there is a compensatory elevation in OER. CMRO₂ is depressed only slightly. This is a relatively promising situation, and indicates that increasing the perfusion to affected areas would benefit the patient by increasing nutrient to deprived brain tissue. The other situation is luxury perfusion, in which the rCBF is decreased to a region, but the perfusion exceeds the metabolic demands of the tissue. There is no increase in OER and CMRO₂ is significantly depressed. This is a dire situation, because it indicates that the tissue is infarcted, and that intervention to increase blood flow to the already dead tissue has no benefit.

A condition that predisposes to stroke is the occurrence of transient ischemic attacks (TIA). TIA are caused by atherosclerotic lesions on large vessels that occlude blood flow to the brain. Detrimental effects are minimized by collateral flow to the affected regions, and the prognosis is more severe when there are multiple lesions that interfere with collateralization. Oxygen-15 studies of TIA patients show that in the occluded regions there is a decrease in CBF and CMRO₂, and an increase in OER and CBV.¹⁷ It has been suggested that an index of TIA severity is the ratio CBF/CBV, with the ratio decreasing in the rank order control > unilateral > bilateral TIA. Using this ratio, TIA patients have been categorized as a mild form with decreased CBF/CBV and a normal OER, and a more severe form in which CBF/CBV is much lower and the OER is increased. Infarcted tissue is distinguished from the more severe form of TIA in that the OER is not increased.

**ACTIVATION STUDIES**

Activation studies refer to PET methodologies to examine the regional function of the brain during human cognitive processes. Processes that have been investigated include visual imagery, learning and recognition, word processing, attention systems and emotions (see Table 5). PET activation studies are a unique research tool with which to unravel the manner in which the brain performs during mental activity.

<table>
<thead>
<tr>
<th>Table 5. Selected Mental Processes Studied with PET Activation Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual imagery</td>
</tr>
<tr>
<td>Auditory signaling</td>
</tr>
<tr>
<td>Single word processing</td>
</tr>
<tr>
<td>Learning</td>
</tr>
<tr>
<td>Memory</td>
</tr>
<tr>
<td>Attention systems</td>
</tr>
</tbody>
</table>

The basis behind PET activation procedures is that an external stimulus or task induces work in a specialized region of the brain. By experimental design of appropriately-controlled conditions in which a single stimulus or task is presented to a subject, the work induced in particular regions of the brain can be identified using PET.

A key issue in activation studies is the technique that is employed to measure brain work. Generation of the electrical signals involved in neuronal pathways induce enhanced metabolic requirements within the relevant brain regions. Metabolic measurements with [¹⁸F]FDG/PET are generally inappropriate for activation studies because they are slow relative to brain response, and repeat studies in a single imaging session are not possible. Likewise, determination of rCMRO₂ by PET is cumbersome, as multiple scans to determine rCBF, rOER, and rCBV are required in the methodology.

The methodology of choice for determination of brain work in PET activation studies is measurement of rCBF.¹⁸ Determination of rCBF by PET is relatively rapid, requiring only a single PET scan over a few minutes. Several repeated studies can therefore be performed within a single imaging setting. This allows for much greater control of experimental conditions. Besides this advantage, measurement of rCBF is actually a more sensitive measurement of brain work than the corresponding metabolic measurement CMRO₂. Although rCBF and rCMRO₂ are correlated during the resting state, there is a focal physiological uncoupling of blood flow and oxidative...
movement during brain stimulation. This results in a much greater increase in rCBF compared to rCMRO₂ during activation experiments (30% vs. 5%). Thus, not only are PET activation studies using [¹⁸O]water procedurally simpler, but they also result in enhanced image contrast.

Because the living brain is always at work, the activation methodology requires a measurement of the rCBF of the brain in the resting state as well as when stimulated to the activated state. The brain regions recruited to perform the task at hand are identified by subtracting the resting CBF measurement from the activated image. Focal sites of enhanced rCBF are readily apparent. By co-registering the PET images with MRI scans of the same subject, the precise anatomical location of the focal activation sites are identified.

It is important to have carefully-controlled conditions when performing PET activation studies to assure that any changes in rCBF are due to the stimulus designed in the experiment, rather than due to spurious external stimuli. The stimulus or task that is used for the activation protocol should be simple so that a specific neuronal pathway is stimulated, rather than generating multiple levels of brain response. For optimized imaging results, the stimulus should also be designed to induce a maximized cerebral response within the particular neuronal pathway being investigated.

PET activation studies have been very successful in improving our understanding of the physiology of human cognition. A limitation of the technique, however, is that the PET measurements only indicate regions of the brain that are recruited for specific tasks. What they do not determine is whether the neuronal signals that are generated by these brain tissues are inhibitory or stimulatory in nature. This information needs to be ascertained through alternative research methodologies.

**MOVEMENT DISORDERS**

Movement disorders include a myriad of involuntary movements such as tremor, chorea, dystonia, tics, and myoclonus. Specific diagnosis of movement disorders is difficult from these clinical signs. There has been considerable effort toward the application of PET for improved diagnosis and to better understand the pathophysiology of disorders. Parkinson’s disease, Huntington’s disease, progressive supranuclear palsy, olivopontocerebellar atrophy, and dystonia have been investigated using PET. Characteristic PET findings that have been noted for these conditions are given in Table 6.

Parkinson’s disease (PD) derives from cell loss or depletion within the striatal pathways of the brain, resulting in tremor, rigidity and bradykinesia. The etiology of this disease is unknown, and therapy is directed at replacement of synaptic dopamine through administration of L-dopa. Oxygen-15 studies have shown that there is an increase in rCMRO₂ in the diseased side of the basal ganglia of asymmetric PD patients, but not in patients with symmetric PD. Levodopa treatment was not found to increase either rCBF or rCBV in the basal ganglia on follow-up studies, suggesting that the beneficial effect of this drug is probably not due to a cardiovascular mechanism. Metabolic studies using [¹⁸F]FDG show that there is a global decrease in CMRG associated with PD that correlates with independent measures of bradykinesia, although the regional pattern of tracer localization does not differ from control images.

The most direct PET measures of the pathological changes that occur in PD have been accomplished using [¹⁸F]FD as a tracer to estimate dopaminergic neuron numbers. There is decreased accumulation of the tracer in the putamen, but not caudate nucleus, of patients with PD compared to controls. Dopaminergic pathways in the putamen are involved in movement, whereas the caudate nucleus is involved in the cognitive effects of dopamine. The [¹⁸F]FD defect thus has an anatomic basis, and there is decreased accumulation in the contralateral putamen in asymmetric PD. In contrast, the putamen of both sides of the brain are affected in bilateral PD. Although there is an age-dependent decrease in the striatal accumulation of [¹⁸F]FD, the rate of decrease in subjects with PD is significantly greater than that in age-matched healthy controls.

Huntington’s disease (HD) is an autosomal dominant disorder that is associated with both choreiform movements and dementia. The neurochemical defect in Huntington’s disease is currently unknown. Although CT demonstrates no remarkable findings, patients with the disorder are readily identified by [¹⁸F]FDG/PET as reduced localization of the radiotracer within caudate. The results of PET studies show that caudate CMRG is significantly decreased in HD compared to healthy controls, and that this decrease in metabolic activity can be used to stage disease severity. The decrease in caudal CMRG that is seen in HD is not identified in Alzheimer’s disease (AD), PD, or depression, so this image defect may help distinguish this dementia from these other common brain disorders. PET measurement of rCMRG can also be used to identify subjects at risk for development of HD.

It is interesting to note that, unlike the case for PD, there is not a decrease in striatal accumulation of [¹⁸F]FDG associated with HD. This is a valuable adjunct to genetic mapping, because these laboratory assays frequently give false negatives for heterozygotes due to recombination.
Table 6. Movement Disorders Studied with PET

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Radiopharmaceutical</th>
<th>Image Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s Disease</td>
<td>[18F]Fluorodopa</td>
<td>Decreased localization in striatum</td>
</tr>
<tr>
<td>Huntington’s Disease</td>
<td>[18F]Fludeoxyglucose</td>
<td>Decreased CMRG in striatum</td>
</tr>
<tr>
<td>Progressive Supranuclear Palsy</td>
<td>[18F]Fludeoxyglucose</td>
<td>Frontal CMRG hypometabolism</td>
</tr>
<tr>
<td>Olivopontocerebellar Atrophy</td>
<td>[18F]Fludeoxyglucose</td>
<td>Cerebellar CMRG hypometabolism</td>
</tr>
</tbody>
</table>

ciated with HD.\(^2\) This PET methodology thus has little utility for evaluation of HD. Preliminary studies with the D2 receptor-binding radioligand \[^{11}C\]N-methylspiperone suggests some promise to the application of this technique,\(^26\) but follow-up studies are absent.

Progressive supranuclear palsy (PSP) is another movement disorder that has been studied by PET. Patients with PSP may present with parkinsonian symptoms, but they do not respond to l-dopa therapy, and the disease progresses rapidly. Unfortunately, it is difficult to clinically distinguish PSP from PD. Regional CMRG is decreased in PSP compared to healthy controls, most dramatically in the motor cortex, striatum, thalamus and cerebellum.\(^27\) Correlations between motor impairment and caudate CMRG have been made, as well as cortical CMRG and duration of disease.\(^28\) Preliminary studies have indicated that associated with PSP is decreased CMRO\(_1\) in cortex and basal ganglia, decreased striatal accumulation of \[^{18}F\]FD (although less of a decrease than with PD), and decreased D2 receptor binding.\(^29\)

Olivopontocerebellar atrophy (OPCA) is a movement disorder characterized by ataxia of gait and speech impairment. It is also associated with dementia, and has several biochemical profiles. A hallmark PET finding with this disease is that compared to controls, OPCA patients have substantially decreased CMRG in the cerebellum and brainstem.\(^30\) A correlation has been found between the decrease in cerebellar CMRG and independent measures of ataxia.

PSYCHIATRY AND DEMENTIA

Numerous types of psychiatric disorders and dementia have been investigated by PET. Psychiatric disorders that have been studied include schizophrenia, depression, anxiety, and panic disorder. Dementias such as Alzheimer’s disease, Huntington’s disease, multi-infarct dementia Pick’s disease, and AIDS-related dementia have also been examined by PET. Each of these disorders has unique pathophysiology, which is reflected in the PET findings.

Psychiatric symptoms can result from either an exaggerated aberration of mental function, or a loss of brain function, and can be categorized as either positive (hyperactive) or negative (hypoactive). Positive psychiatric symptoms include hallucinations, delusions, or bizarre behavior, whereas negative psychiatric symptoms include aloxia, blunted affect, avolition, asociality, and attentional impairment. It is believed that the positive psychiatric symptoms involve the frontal and limbic regions of the brain, and the causative neural mechanism may be an irritative lesion, a deactivated regulatory center, or disconnection of neural circuits. Negative symptoms, by contrast, involve the prefrontal cortex, and the relevant neural mechanism is thought to be neuronal loss.

Structural imaging of schizophrenia results in nonspecific diagnostic information. There is ventricular enlargement with cortical and cerebellar atrophy. PET is a more appropriate imaging technique for schizophrenia because it gives functional information about the condition before structural changes occur. PET findings of patients with schizophrenia are explained to a large extent by the dopamine hypothesis of schizophrenia.\(^31\) The major projections of the dopaminergic system are from the substantia nigra into the basal ganglia and limbic system (nigrostriatal tract), with another branch projecting to the frontal lobe of the brain (mesocortical tract). It is hypothesized that stimulatory signals from the nigrostriatal tract may be responsible for the positive symptoms of schizophrenia, while inhibitory signals from the mesocortical tract may cause the negative symptoms of the condition.

Functional imaging of schizophrenia has included measurement of regional perfusion, CMRG, and dopamine D2 receptor binding (see Table 7). Several studies have shown that there is hypofrontality of rCBF, with the frontal/posterior CBF ratio significantly decreased in schizophrenics compared to healthy controls. The global CMRG is depressed in schizophrenics, and hypofrontality is evident in the anteroposterior ratio of rCMRG.\(^32\)
Metabolic disconnection in schizophrenics has been noted, with the subcortical/cortical rCMRG ratio in schizophrenics being roughly twice that of controls. This ratio has been suggested as an index of disease severity. In addition to hypofrontality, more recent evidence points to dysfunction of multiple neural structures in schizophrenia. Elevated densities of dopamine D2 receptors in the basal ganglia of schizophrenics has been measured using the receptor-binding tracer \[^{[1]}C\][N-methyl]spiperone. This finding has not been identified when \[^{[1]}C\]raclopride was used, which may be a result of the different receptor-binding characteristics of the two tracers. D2 receptor-binding radiopharmaceuticals have also been used for PET evaluation of antipsychotic therapy of schizophrenia.

### Table 7. PET Imaging of Schizophrenia

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Image Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>[^{[16]}O]Water</td>
<td>Hypofrontality</td>
</tr>
<tr>
<td>[^{[18]}F]FDG</td>
<td>Decreased global CMRG</td>
</tr>
<tr>
<td>[^{[11]}C][N-methyl] spiperone</td>
<td>Increased subcortical/cortical rCMRG</td>
</tr>
</tbody>
</table>

Investigation of depression is hampered by heterogeneity in the study population as well as the confounding effects of medications. Perfusion, metabolic, and receptor-binding PET studies have been performed on drug-free subjects with primary unipolar depression. Selection of this patient population should minimize the effect of confounding variables. The results support a neural model in which depression is associated with dysfunctional interactions between multiple structures, rather than increased or decreased activity in a single region of the brain. PET studies using \[^{[16]}O\]water or \[^{[18]}F\]FDG have shown that rCBF and rCMRG is decreased in various regions of the ventral prefrontal cortex, and increased in the dorsal prefrontal cortex. Application of the serotonin receptor-binding radiopharmaceutical \[^{[18]}F\]altanserin has also shown that serotonin 2a receptor sites are decreased in depression.

There are distinguishing PET findings in the various mood disorders which may facilitate their differential diagnosis (see Table 8). In anxiety disorder, the rCMRG is substantially elevated in the caudate nucleus, unlike healthy controls or subjects with unipolar depression. In contrast, the rCMRG is elevated in the right orbital gyrus in patients with obsessive-compulsive disorder relative to either normals or unipolar depressed subjects. Perfusion studies of phobic fear show increased rCBF in the lateral orbital/anterior insula as well as the lateromedial cerebellum. After habitation to phobia, this selective perfusion pattern is altered such that the posterior orbital cortex has increased rCBF. It is hypothesized that this latter region of the brain is recruited to suppressing the cerebral tissues involved in the phobia response.

### Table 8. Mood Disorders Studied by PET

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Image Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Increased rCBF in orbital cortex</td>
</tr>
<tr>
<td></td>
<td>Increased CMRG in orbital cortex</td>
</tr>
<tr>
<td>Obsessive-Compulsive Disorder</td>
<td>Increased CMRG in striatum</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>Increased CMRG in right orbital gyrus</td>
</tr>
<tr>
<td></td>
<td>Increased rCBF in lateral orbital cortex</td>
</tr>
</tbody>
</table>

Dementia is another form of mental impairment that has been extensively studied by PET. Some of the key metabolic findings that have been noted are shown in Table 9. Dementia can be defined as a progressive decrease in the cognitive, intellectual and memory functions of the patient. The most common form of dementia is AD. It has been estimated that 55% of all dementias are of the AD category. Multi-infarct dementia (MID) is a different form of the disorder, and accounts for approximately 15% of the total cases. Another 15% of dementias is a combination of AD and MID.

### Table 9. Dementias Studied using \[^{[18]}F\]FDG/PET

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Image Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's Disease</td>
<td>Decreased cortical rCMRG</td>
</tr>
<tr>
<td></td>
<td>Asymmetry in rCMRG</td>
</tr>
<tr>
<td>Multi-Infarct Dementia</td>
<td>Focal hypometabolism</td>
</tr>
<tr>
<td>Pick's Disease</td>
<td>Frontal hypometabolism</td>
</tr>
<tr>
<td>Huntington's Disease</td>
<td>Decreased striatal CMRG</td>
</tr>
<tr>
<td>AIDS-related Dementia</td>
<td>Decreased global CMRG</td>
</tr>
</tbody>
</table>

The prevalence of dementia increases late in life, and functional imaging of this condition must account for physiological changes that occur in the healthy aging brain. The alterations of brain physiology that are associated with dementia parallel these changes in normal aging, and are not unique to the disease itself. In the healthy brain, there is a gradual decrease in rCBF, CMRO2, and CMRG as the age of the subject increases. Moreover, it has been noted that associated with the aging process is hypofrontality of glucose utilization; as the subject ages, the decrease in rCMRG in the frontal cortex exceeds that in other cortical zones. It is therefore important to have age-matched controls when identifying image defects in
patients with dementia. 

[18F]FDG/PET studies of AD have shown that there are significant changes in rCMRG that correlate with disease severity. When absolute values of rCMRG are examined, substantial decreases are seen in the frontal, parietal, temporal, and occipital cortex of patients with the severe form of AD. In subjects with the mild-moderate form of the disease, however, statistical significance is not achieved in the difference between rCMRG in these cortical tissues compared to that of controls. In order to index disease severity, absolute values of rCMRG are examined, and significant changes in rCMRG that correlate with disease severity are found in the temporal and occipital cortex of patients with dementia. 

The ratio of rCMRG in the parietal cortex during AD has a modest correlation with independent measures of mental impairment. There have also been attempts to correlate the left-right asymmetry of rCMRG in the brain of AD patients with disease severity. These have met with varying degrees of success.

There are a variety of less prevalent dementias that illustrate unique metabolic patterns in functional PET imaging. This facilitates their differentiation from AD, as well as from each other. In some cases, it may also make therapeutic benefit possible through the monitoring of disease progression. Multi-infarct dementia (MID), involves a stepwise clinical deterioration of the patient that is clinically similar to AD. Neuro-PET images of the brains of patients with MID, however, are characterized by focal hypometabolism. This finding allows MID to be readily distinguished from AD in [18F]FDG/PET scans. Another dementia that is clinically similar to AD is Pick's disease. Pick's disease is characterized by frontal hypometabolism, so this disorder can also be differentiated from AD using [18F]FDG/PET scans. As mentioned in the section on movement disorders, a hallmark of Huntington's disease (HD) is decreased rCMRG in the basal ganglia, which correlates with a decrease in verbal learning ability. This selective hypometabolism can be used in differential diagnosis, as well as in staging disease severity. Functional imaging of AIDS-related dementia shows that a stepwise global nonfocal decrease in CMRG is associated with disease severity.

IN VIVO PHARMACOLOGY

Positron emission tomography methodologies offer unique opportunities for the investigation of neuropharmacology in vivo. These imaging applications are far-reaching, ranging from preclinical studies using animal experiments, to routine clinical examination of human subjects in clinical trials.

From the perspective of preclinical studies using PET, this methodology offers special advantages. For the testing of centrally-acting agents in animals preceding human application, nonhuman primates are preferred due to their genetic similarity to man. PET is a valuable research tool in this regard, because this imaging technique makes possible repeat studies within the same individual animal. This is advantageous, because serial imaging of the same animal subject does not introduce inter-individual variables. Preclinical studies in animals are virtually the only way novel tracer techniques can be fully validated prior to application to human subjects. Animal experiments allow for carefully-controlled conditions for optimization of new methodologies that are subsequently applied to human subjects in the clinical setting.

Pharmacology can be studied in vivo in one of two manners. The most direct method is to label the drug to be investigated with a positron-emitting nuclide, and then evaluate its distribution in vivo using PET imaging. This approach is limited to those molecular structures that have functional groups that lend themselves to radiosynthesis with carbon-11 or fluorine-18. This approach has been especially successful in the application of receptor-binding radioligands for tracer kinetic analysis. This PET methodology allows the in vivo measurement of the binding of the various labeled drugs to their targeted neuroreceptor sites. This approach has been successfully employed for PET evaluation of brain receptor changes in several neurological disorders, including epilepsy (benzodiazepine receptors), schizophrenia (dopamine D2 receptors), and depression (serotonin 2a receptors).

The above method requires that each drug to be studied be prepared in radioactive form. A second more general method of studying pharmacology in vivo by PET is to measure the effect of unlabeled drugs on the in vivo behavior of established PET radiopharmaceuticals. In this way, virtually any centrally-acting drug can be evaluated for its pharmacological effect on cerebrovascular parameters (rCBF, rCBV), cerebral metabolism (rCMRO2, rCMRG), or receptor binding (using the receptor-binding radiopharmaceuticals listed in Table 2).

This approach to PET study of pharmacology is much more versatile than the method of labeling each individual drug structure, because many therapeutically-useful drugs simply do not make good radiopharmaceuticals. Their chemical structure may not lend themselves to labeling with a short-lived positron-emitting nuclide. Their pharmacokinetics may be inappropriate for PET imaging due to slow clearance, high non-specific uptake in the brain, or binding to multiple receptor sites in a non-selective manner. However, by administering such clinically-used drugs along with validated PET tracers, analysis of their effects on specific brain parameters can be quantified using PET methodology.

Both methodologies have been employed with PET to assess the pharmacological effect of drugs in treating the many disease categories discussed above. In addition to
these clinical studies, PET methodology has also been employed for evaluation of drugs of abuse (Table 10). The cerebral localization of [11C] cocaine onto the dopamine transporter of neurons within the basal ganglia has been visualized with PET, and the tracer kinetics have been compared to the rate of onset of euphoria caused by the drug. In cocaine abusers, decreased rCBF has been noted in the frontal cortex, secondary to the vasoconstrictive actions of cocaine. rCMRG in cocaine abusers is increased, although this altered metabolic pattern appears to be reversed after several drug-free days. Transient alterations in dopamine D2 receptor binding and [18F]FD accumulation in striatum have also been noted.

Table 10. Drugs of Abuse Studied by PET

<table>
<thead>
<tr>
<th>Abused Drug</th>
<th>Parameters Investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>[11C]Cocaine cerebral kinetics</td>
</tr>
<tr>
<td></td>
<td>rCBF</td>
</tr>
<tr>
<td></td>
<td>rCMRG</td>
</tr>
<tr>
<td></td>
<td>D2 receptor binding</td>
</tr>
<tr>
<td></td>
<td>[18F]FD accumulation</td>
</tr>
<tr>
<td>Alcohol</td>
<td>rCMRG</td>
</tr>
<tr>
<td>Nicotine</td>
<td>[14C]Nicotine cerebral kinetics</td>
</tr>
<tr>
<td>Marijuana</td>
<td>rCMRG</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>rCMRG</td>
</tr>
</tbody>
</table>

PET imaging of alcoholics has been performed as well. The results show evidence of decreased CMRG in the cerebral cortex of chronic alcoholics. This hypometabolism was reversible, with glucose utilization rates returning to normal after several alcohol-free days. In a type of drug challenge study, the decrease in CMRG was found to be greater in alcoholics than in control subjects upon intravenous administration of an acute dose of ethanol.

PET has in addition been employed in preliminary studies designed to evaluate changes in cerebral physiology that are induced by chronic use of marijuana, nicotine, or phencyclidine. Further studies are needed before any conclusions can be drawn regarding the pathophysiology of these events, however.

CONCLUSIONS

Positron emission tomography is a valuable clinical tool for the functional imaging of the human brain. PET methodologies exist for noninvasive assessment of several cerebral physiological parameters, including cerebrovascular, metabolic, and receptor-binding measurements. This imaging technique increases our understanding of normal and pathological processes within the brain, and aids in therapeutic decision-making. The continuously-evolving specialty field of neuro-PET offers exciting career opportunities for nuclear pharmacists working with other health care professionals in this area.

REFERENCES


QUESTIONS

1. An advantage of PET over alternative methods for imaging the brain is
   a. simplicity
   b. image resolution
   c. acquisition of functional data
   d. cost

2. Quantitative PET imaging requires
   a. attenuation correction
   b. cross-calibration
   c. phantom correction
   d. all of the above

3. $[^{18}O]$Water is used for PET measurement of
   a. rCBF
   b. rCBV
   c. rCMRO$_2$
   d. rCMR$_G$

4. Which of the following is NOT a receptor-binding PET tracer?
   a. $[^1]C$Raclopride
   b. $[^8]F$Fluorodopa
   c. $[^8]F$Alanserin
   d. $[^1]C$(N-methyl)spiperone
5. $K_d$ and $B_{max}$ are parameters that can be derived from PET studies with

a. $[^{15}O]$Water  

b. $[^{18}F]$Fluorodopa  

c. $[^{18}F]$Fludeoxyglucose  

d. $[^{18}F]$Flumazenil

6. $[^{18}F]$FDG localization in epileptic foci is

a. decreased during the interictal phase / increased during the ictal phase  

b. increased during the interictal phase / decreased during the ictal phase  

c. decreased during the interictal phase / decreased during the ictal phase  

d. increased during the interictal phase / increased during the ictal phase

7. A limitation of $[^{18}F]$FDG/PET for evaluation of brain tumors is that it does not

a. demonstrate metabolically-active areas  

b. differentiate active tumor from edematous areas  

c. distinguish medium- and low-grade tumors  

d. all of the above

8. The PET tracer that most directly measures neuronal cell loss in Parkinson’s disease is

a. $[^{15}O]$Water  

b. $[^{11}C]$Raclopride  

c. $[^{18}F]$Fludeoxyglucose  

d. $[^{18}F]$Fluorodopa

9. The correlation between decreased $[^{18}F]$FD accumulation and motor impairment is strongest in which brain tissue?

a. putamen  

b. caudate nucleus  

c. frontal cortex  

d. thalamus

10. CMRG within the striatum is decreased in

a. Alzheimer’s disease  

b. Bipolar disorder  

c. Huntington’s disease  

d. Parkinson’s disease

11. $[^{18}F]$Fluorodopa accumulation within the striatum is decreased in

a. Alzheimer’s disease  

b. Parkinson’s disease  

c. Bipolar disorder  

d. Huntington’s disease

12. A characteristic finding in Progressive supramolecular palsy is

a. decreased CMRG in the frontal cortex  

b. decreased cortical CMRO$_2$  

c. decreased $[^{18}F]$Fluorodopa within striatum  

d. all of the above

13. Decreased CMRG within the cerebellum is associated with

a. Parkinson’s disease  

b. Olivopontocerebellar atrophy  

c. Progressive supramolecular palsy  

d. Alzheimer’s disease

14. The transition from ischemia to infarction involves

a. increase in perfusion reserve  

b. an increase in OER  

c. irreversible tissue damage  

d. all of the above

15. Transient ischemic attacks

a. predispose to Alzheimer’s disease  

b. involve atherosclerotic lesions of small vessels only  

c. have an effect that is aggravated by collateral flow  

d. have more severe consequences with multiple lesions

16. Limitations of $[^{18}F]$FDG for evaluation of stroke include:

a. Quantification of CMRG is a relatively lengthy procedure  

b. Changes in CMRG are less than changes in CMRO$_2$  

c. CMRG may increase due to anaerobic glycolysis  

d. All of the above
17. The most sensitive PET measurement of "brain work" is
   a. CMRO₂
   b. CMRG
   c. rCBV
   d. rCBF

18. The greatest limitation of PET activation studies is
   a. image resolution
   b. need for carefully-controlled conditions
   c. limited complexity of stimulus
   d. does not distinguish between excitatory/inhibitory signals

19. PET findings associated with schizophrenia include
   a. increased striatal binding of [¹¹C](N-methyl)spiperone
   b. CMRG hypofrontality
   c. rCBF hypofrontality
   d. all of the above

20. The severity of Alzheimer's disease is most closely related to changes in CMRG in the
   a. frontal cortex
   b. parietal cortex
   c. temporal cortex
   d. occipital cortex

21. Multi-infarct dementia is most easily recognized in [¹⁸F]FDG/PET images as
   a. hypofrontality
   b. global hypometabolism
   c. focal hypometabolism
   d. parietal hypometabolism

22. The dementia characterized by frontal CMRG hypometabolism is
   a. Alzheimer's disease
   b. Pick's disease
   c. Huntington's disease
   d. Multi-infarct dementia

23. Caudal CMRG hypometabolism in Huntington's disease
   a. identifies subjects at risk for development of symptoms
   b. correlates with tests of verbal cognition
   c. can be used to stage disease progression
   d. all of the above

24. [¹¹C]Flumazenil is used for PET evaluation of
   a. schizophrenia
   b. bipolar disorder
   c. epilepsy
   d. ischemia

25. Cocaine users have altered
   a. receptor binding by [¹¹C] (N-methyl)spiperone
   b. CMRG
   c. striatal accumulation of [¹⁸F]FDG
   d. all of the above