2-Deoxy-2-[^{18}F]Fluoro-D-Glucose and Alternative Radiotracers for Positron Emission Tomography Imaging Using the Human Brain as a Model

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2-Deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG) is now routinely available in many hospitals and other institutions either via on-site production or from one of the dozens of regional radiopharmacies worldwide. Its reliable production has opened the possibility for use in both basic and clinical investigations and also in pairing it with other more biologically specific positron emission tomography tracers to provide an important functional perspective to the measurement. In this article, we highlight examples in which ^{18}FDG is paired with another carbon-11- or fluorine-18-labeled radiotracer in the same subject to correlate neurotransmitter-specific effects with regional metabolic effects using the human brain as a model. We describe studies that fall into three major areas: normal aging, neuropsychiatric disorders, and drug action.

THE BRAIN BREAKS down glucose during glycolysis, producing adenosine triphosphate and providing the energy that drives neurotransmission and signal transduction. Because almost all of the brain's energy derives from glucose metabolism, the development of 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG), a radiotracer that measures brain glucose metabolism, nearly 30 years ago has had a profound influence on research in the neurosciences and on the evolution of positron emission tomography (PET).[1] It was first synthesized via an electrophilic fluorination with fluorine-18-labeled elemental fluorine.[2] Later, a high-yield nucleophilic route using fluorine-18-labeled fluoride ion was introduced, making it possible to produce large quantities of ^{18}FDG.[3] Although no major new developments have been made in the synthesis of ^{18}FDG following the nucleophilic route, a number of variants have been investigated to improve the displacement and the deprotection steps, and considerable effort has been put into fine-tuning the reaction and to identifying impurities and contaminants that are carried through to the final product.[4] This has become more critical with the increasing use of ^{18}FDG in clinical practice, where the documentation of the pharmaceutical quality of the product is required. In addition, there are now a number of commercial ^{18}FDG synthesis modules that reduce the burden to chemists charged with the day-to-day burden of reliably producing large quantities of pharmaceutical quality product.[5]

These developments and the remarkable properties of ^{18}FDG have largely overcome the limitations of the 110-minute half-life of fluorine-18, and ^{18}FDG is currently available to most regions of the United States from a number of central production sites. This avoids the need for an on-site cyclotron and chemistry laboratory and has opened up the use of ^{18}FDG to institutions that have a PET scanner (or other imaging device) but no cyclotron or chemistry infrastructure. Currently, ^{18}FDG is used by many hospitals as an "off-the-shelf" radiopharmaceutical for clinical diagnosis in heart disease, in seizure disorders, and in oncology, the area of most rapid growth.[6] However, its ready availability, either from the parent institution or through a regional radiopharmacy, has opened the possibility of also using it in more widespread applications in the human neurosciences, including neuropsychiatric diseases and in drug research and development.[7]

In this article, we highlight examples in which an ^{18}FDG scan and at least one other PET radiotracer scan[8] are performed on the same subject to investigate the functional correlates of neurotransmitter activity using the human brain as a model. The studies covered fall into three major areas: normal aging, neuropsychiatric disorders, and drug action and provide a more complete perspective on brain function and its relationship to disease, drug action, and behavior than the use of either ^{18}FDG or other radiotracers alone.

NORMAL AGING

The progressive increase in the number of elderly individuals and the increased rate of neuro-

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degenerative diseases with increasing age has created the need to understand the molecular changes that occur in the human brain during aging and their relationship to behavior and cognition. Although it has long been thought that there is significant neuronal loss during normal human aging, modern cell-counting techniques and better premortem characterization of humans who later came to autopsy have largely disputed this.[9] At the heart of this discrepancy is speculation that in older studies, normal samples had probably been contaminated by the inadvertent inclusion of demented individuals.[10] Today, there is evidence that neuron number in the entorhinal cortex is largely maintained during normal aging, although there is shrinkage in neuron size and a significant increase in glial cell number with normal aging.

The Brain Dopamine System

Even though neuron numbers largely remain intact during normal aging, loss of dopaminergic innervation of the striatum is a prominent age-related change that corresponds to the loss of dopamine cell bodies in the substantia nigra.[11] There are many PET studies in normal aging investigating the brain dopamine system from the perspective of measuring changes in dopamine receptors, transporters, and dopamine metabolism as well as changes in brain glucose metabolism.[12] Early PET studies in normal aging with ^{18}FDG reported decrements in brain function predominantly in frontal cortex and the cingulate gyrus.[13] These changes are observed even in relatively young subjects.[14] Other neurotransmitter systems have also been investigated with a variety of different radiotracers.[15]

To determine whether age-related changes in the brain dopamine system are associated with age-related decrements in glucose metabolism in the frontal cortex and cingulate gyrus, a multi-tracer investigation of 37 healthy volunteers aged 24 to 86 years was performed with [^{11}C]*d-threo*-methylphenidate to measure dopamine transporter availability, [^{11}C]raclopride to measure dopamine D2 receptor availability, and ^{18}FDG to measure brain function. Each subject also had neuropsychological testing. Brain dopamine D2 receptor and brain dopamine transporter levels were correlated in individuals: those having high dopamine receptors also had high dopamine transporters, and this correlation was maintained after removing age effects.[16] Correlation analysis between dopamine D2 receptor availability and brain glucose metabolism revealed significant correlations between metabolism and D2 receptors in the frontal cortex, anterior cingulate gyrus, temporal cortex, and caudate.[17] These correlations also remained significant after removing age effects (partial correlation). This multi-tracer study provides a new perspective on the brain as an interacting system and provides the first link between age-related declines in brain dopamine activity and frontal cortex and cingulate gyrus metabolism. Understanding the role that the degeneration of the dopamine system has on the function of the human brain and its contribution to the neurobehavioral changes in the elderly will enable the development of interventions targeted toward ameliorating these changes and retarding their presentation. It also provides an essential context for the investigation of the dopamine system in neuropsychiatric illnesses and their evolution with age.

Monoamine Oxidase B (MAO B)

Many neuronal cells and their associated neurotransmitters and enzymes show age-related losses.[18] However, several postmortem assays of human brain MAO B report increases with age and in neurodegenerative disease.[19] Age-related increases in MAO B are consistent with the known presence of MAO B in glial cells[20] and with reports that the number of glial cells increases with age in the normal human brain[9] and in neurodegenerative disease and brain injury.[21] There is speculation that increases in brain MAO B with aging results in increases in oxidative stress and that this may play a role in the vulnerability of the brain dopamine system to age-related degeneration.[22]

To examine the feasibility of using MAO B imaging for detecting and tracking glial cell proliferation accompanying aging and neurodegenerative processes in the living human brain, MAO B was measured in a group of 21 normal healthy human subjects (age range 23-86) using deuterium substituted [^{11}C]L-deprenyl ([^{11}C]L-deprenyl-D2) and PET.[23] Brain glucose metabolism was also measured with ^{18}FDG in 15 of the subjects. MAO B was elevated ($P < 0.004$) in all brain regions examined except the cingulate gyrus. In contrast, subjects showed the expected regional age-related decreases in metabolism in the frontal cortex and cingulate gyrus. In the 15 subjects in whom both

MAO B and glucose metabolism were measured, there was a trend ($P < 0.03$) toward an inverse association between brain glucose metabolism and MAO B activity in the frontal and parietal cortices consistent with the hypothesis that increases MAO B concentration would be associated with glial cell proliferation and reduced brain glucose metabolism.

NEUROPSYCHIATRIC DISORDERS

Parkinson's Disease (PD) and Other Movement Disorders

PD affects 1% of the population over the age of 65. The disease is caused by a loss of dopaminergic neurons in the substantia nigra and is characterized by rigidity, tremors, and bradykinesia. Its cause is unknown and the early symptoms may be similar to other movement disorders. Multi-tracer PET studies have been performed in PD to investigate the relationship between brain dopamine activity and brain metabolism and their relationship to symptoms. These studies have also been useful in making differential diagnoses between PD and other movement disorders when symptoms are ambiguous and in understanding the underlying molecular deficits corresponding to specific symptoms. For example, ^{18}FDG and [^{18}F]fluorodopa (to measure dopamine metabolism) scans have been combined in the same patients along with clinical measures for bradykinesia, rigidity, tremor, gait disturbance, left-right asymmetry, dementia, and overall disease severity.[24] Patterns were extracted from the ^{18}FDG scans using a scaled subprofile model and [^{18}F]fluorodopa scans were analyzed by calculating an influx constant (K_i). In the PD patients K_i values correlated with individual measures of bradykinesia and gait disability. Scaled subprofile model analysis of ^{18}FDG images showed a distinct pattern of regional metabolic asymmetries, which correlated with motor asymmetries ($P < 0.001$) and left-right differences in K_i ($P < 0.01$). The authors suggest that the unique and complementary information about PD can be obtained from paired studies of ^{18}FDG and [^{18}F]fluorodopa.

The relationship between monosymptomatic resting tremor (mRT) and PD has been investigated using a multi-tracer approach with ^{18}FDG, [^{18}F]fluorodopa, and [^{11}C]raclopride.[25] The studies were performed in eight mRT patients who showed all three classic parkinsonian symptoms and seven age-matched healthy subjects. PD and mRT patients did not show significant differences in any of the radiotracer measurements. However, there were significant differences between the pooled patient data (mRT and PD) and control subjects in anterior and posterior putamen ipsilateral and contralateral to the more affected body side, and ipsilateral and contralateral putaminal gradients of the influx constant (K_i) values. Normalized glucose values of the whole cerebellum were reduced in the PD but not the mRT groups relative to controls. The authors suggest that mRT represents a phenotype of PD in which both have a similar striatal dopaminergic deficit and postsynaptic D2-receptor upregulation whereas cerebellar hypometabolism in PD is more closely related to akinesia and rigidity rather than to tremor.

^{18}FDG and [^{18}F]fluorodopa have recently been explored to differentially diagnose multiple-system atrophy and idiopathic PD.[26] This is often a difficult distinction because of the presence of signs and symptoms common to both forms of parkinsonism, particularly at early stages. The frontal, temporal cortex glucose metabolism as well as metabolism in the caudate, putamen, cerebellum, and brainstem in multiple-system atrophy patients was significantly lower than in the controls; however the accuracy of the ^{18}FDG for differentiation was lower than that of [^{18}F]fluorodopa. The authors conclude that glucose metabolism is useful for assessing regional metabolic activity whereas [^{18}F]fluorodopa is useful for differentiating between multiple-system atrophy and PD. A more recent study reported the results of an investigation of the metabolic changes in early multiple system atrophy combining ^{18}FDG and 6-[^{18}F]fluorodopa.[27] In these early patients, glucose metabolism was normal in cortical regions but decreased in cerebellum, brainstem, and striatum relative to normal controls. In addition the severity of extrapyramidal symptoms correlated with striatial [^{18}F]fluorodopa uptake but not with striatal glucose metabolism, indicating that nigral damage and not striatal dysfunction may contribute to extrapyramidal symptoms in early multiple-system atrophy.

Another multi-tracer PET investigation with ^{18}FDG, [^{18}F]fluorodopa and [^{11}C]raclopride in normal controls, PD patients, and patients with multiple-system atrophy reported that striatal [^{18}F]fluorodopa values separated all healthy subjects from patients with parkinsonism but was not

useful in distinguishing those patients with multiple-system atrophy from PD.[28] However, striatal [^{11}C]raclopride binding as well as ^{18}FDG values discriminated all patients with multiple-system atrophy from PD patients as well as from healthy control subjects. These data suggest that both ^{18}FDG and [^{11}C]raclopride are useful in assessing striatal function and may be useful characterizing patients with multiple-system atrophy whereas [^{18}F]fluorodopa measurements accurately detect abnormalities of the nigrostriatal dopaminergic system but may not distinguish among different forms of parkinsonism.

Epilepsy

Glial cells are greatly elevated in neurodegenerative disorders, including Alzheimer's disease, seizure disorders, and also during normal aging. Because MAO B is localized in glial cells, it is a potential marker for gliosis and sites of brain injury. In fact, deuterium-substituted [^{11}C]L-deprenyl, a specific tracer for MAO B, has been used in conjunction with ^{18}FDG to map gliosis and metabolism in the same brain region in patients with focal epilepsy.[29] There were 23 patients, 14 with mesial temporal lobe epilepsy and 9 with seizures of neocortical origin. Six normal healthy controls were used as a comparison group. Each subject had a scan with [^{11}C]L-deprenyl-D2 and ^{18}FDG to assess asymmetries in [^{11}C]L-deprenyl-D2 distribution volume and in ^{18}FDG uptake in the three groups. There were significant differences between the epileptogenic and contralateral temporal lobe in the patients with temporal lobe epilepsy but not those with seizures of neocortical origin nor the control group. The authors suggest PET with [^{11}C]L-deprenyl-D2 is a useful method for identifying temporal lobe lesions but not neocortical lesions. Here the [^{11}C]L-deprenyl scan shows elevated MAO B (and presumably gliosis) in brain regions where ^{18}FDG shows hypometabolism thereby enhancing the information provided by either scan alone.

Alzheimer's Disease

Alzheimer's disease affects 4 million people in the United States alone, and currently it affects 35% of the population over the age of 85. This high rate, the lack of knowledge on the causes, and the lack of effective treatments have stimulated considerable research to understand the neurobiology of the disease and to develop therapies that can either halt or slow its progression. ^{18}FDG has been used with PET to investigate correlations between regional glucose metabolism and symptom severity.[30] These studies reported hypometabolism in parietal and temporal areas and in frontal association areas. And more recently ^{18}FDG has been used to study individuals at genetic risk who carry the APOE-e-4-positive gene and these studies suggest that ^{18}FDG/PET may provide a means to detect early disease.[31] Recently radiotracers with high affinity for neurofibrillary tangles and β-amyloid plaques have been developed, and one of these [^{18}F]FDDP, a hydrophobic radiofluorinated derivative of malononitrile, has been shown to bind specifically to tangles and plaques in vitro.[32] PET studies with [^{18}F]FDDP have been undertaken to determine the feasibility of assessing plaque load in nine Alzheimer's patients and a group of seven control subjects.[33] These measures were coupled with ^{18}FDG scans to determine whether elevations in [^{18}F]FDDP binding and retention were associated with decreased metabolism. Magnetic resonance imaging scans were run to assess atrophy, and memory performance also was assessed. Greater accumulation and slower clearance was observed in plaque and tangle-dense brain areas, and this correlated with memory performance scores. The relative residence time of [^{18}F]FDDP in brain regions affected by Alzheimer's was significantly longer in patients than in control subjects ($P = 0.0007$). In addition, brain areas with low glucose metabolism corresponded to those with high accumulation and retention of [^{18}F]FDDP. These radiotracers provide a strategy for the potential diagnosis of early Alzheimer's disease and also for addressing whether plaque and tangle burden tracks memory and cognitive decline and for monitoring therapies.

Based on evidence that the peripheral benzodiazepine binding site antagonist PK 11,195 increased in areas of microgliosis, including the temporal association cortex of patients with Alzheimer's disease, [^{11}C]PK 11,195 binding was measured in eight patients with a diagnosis of probable Alzheimer's disease.[34] For comparison, cerebral glucose metabolism was also measured with ^{18}FDG. No increases in peripheral benzodiazepine binding were identified in patients with probable Alzheimer's disease, and binding was lowest in regions that were most hypometabolic.

The authors conclude that the postmortem elevations peripheral benzodiazepine binding sites associated with microgliosis and cellular inflammation in Alzheimer's disease are undetectable by PET using [^{11}C]PK 11,195 in patients with mild-to-moderate dementia.

Creutzfeldt-Jacob (CJD) Disease

CJD is the human form of a transmissible spongiform encephalopathy. It is neuropathologically characterized by neuronal loss, astrocytosis, spongiform changes and deposits, and brain deposits of a protease-resistant prion protein. Clinical diagnosis, especially in the early stages, when symptoms are ambiguous is problematic. A multitracer study was performed in 15 patients with the symptoms of CJD combining O-15 water to measure blood flow, ^{18}FDG to measure metabolism, and deuterium-substituted [^{11}C]L-deprenyl ([^{11}C]L-deprenyl-D2) to measure MAO B (as an index of astrocytosis).[35] The goal was to detect specific patterns of tracer binding in patients proven to have CJD and also to correlate regional PET patterns with clinical and neuropathological patterns. Patients had a range of disabilities, and some of them needed to be anesthetized for the study. For this reason, a major image analysis strategy was to calculate uptake asymmetry indices (right versus left) rather than to use absolute measures, which would be affected by anesthesia in the case of ^{18}FDG. Another strategy was to look for regions that had both decreased glucose metabolism (indicating decreased neuronal function) that were accompanied by elevations in [^{11}C]L-deprenyl-D2 binding (indicating astrocytosis). Patients with definite or probable CJD showed the predicted simultaneous decreases in glucose metabolism and elevations in [^{11}C]L-deprenyl-D2 binding in specific brain regions including many cortical areas and cerebellum but not temporal cortex. The patterns were different for the other patients and paralleled the neuropathological findings indicating neuronal degeneration and astrocytosis.

Traumatic Brain Injury

PET and single-photon emission computed tomography imaging have documented global and regional decreases in brain blood flow and metabolism in traumatic brain injury.[36,37] MAO B imaging with [^{11}C]L-deprenyl-D2 was combined with ^{18}FDG to determine whether hypometabolic lesions show a corresponding elevation in MAO B presumably reflecting elevated glial cells known to occur in brain injury.[38] Seven patients with traumatic brain injury suffering from seizures and memory loss were scanned with both [^{11}C]L-deprenyl-D2 and ^{18}FDG, and the results were compared with a group of nine normal healthy controls who underwent the same paired scans.[23] The patterns of distribution of metabolism and MAO B in temporal regions were compared in the patients and normal subjects. Hypometabolic regions were identified on the ^{18}FDG scans and MAO B values corresponding to these brain regions were determined. Glucose metabolism was reduced in temporal regions in patients relative to normal subjects. Of the 13 hypometabolic brain regions in the seven trauma patients, six (46%) showed a corresponding elevation in MAO B. There was a trend for a significant inverse relationship between normalized glucose metabolism and normalized MAO B values for medial temporal cortex. Although MAO B images provide a markedly better delineation of the medial temporal regions than ^{18}FDG in both patients and controls, there was not a consistent inverse relationship between metabolism and MAO B similar to that reported in PET studies of epileptogenic temporal lobes with [^{11}C]L-deprenyl-D2 and ^{18}FDG indicating that prospective studies are to determine the pathophysiology of hypometabolic lesions in head trauma.

Obesity

The increasing number of obese individuals in the United States adds urgency to the efforts to understand the mechanisms underlying pathological overeating. Imaging studies using PET implicate the involvement of brain dopamine in the drive for normal and pathological food intake in humans.[39] In normal body weight, fasting subjects, food presentation that could not be consumed was associated with increases in striatal extracellular dopamine, which provides evidence of an involvement of dopamine in nonhedonic motivational properties of food intake.[40] Recent [^{11}C]raclopride/PET measures of dopamine D2 receptor availability in pathologically obese subjects showed reductions in striatal D2 receptor availability that were inversely associated with the body mass index of the subject.[41] The involvement of the dopamine system in reward and reinforcement has led to the

hypothesis that low brain dopamine activity in obese subjects may contribute to pathological overeating. In this same study, each individual who had a [^{11}C]raclopride scan also had an ^{18}FDG scan to assess differences in regional brain metabolism between obese and lean subjects at rest.[42] Interestingly, obese subjects showed significantly higher metabolic activity in the bilateral parietal somatosensory cortex in the regions where sensation to the mouth, lips and tongue are located. The enhanced activity in somatosensory regions involved with sensory processing of food in the obese subjects could make them more sensitive to the rewarding properties of food related to palatability and could be one of the variables contributing to their excess food consumption. The changes in the somatosensory cortex were not linked with the reductions in dopamine D2 receptors, suggesting that they reflect a nondopaminergic process and highlighting the contribution of multiple neurotransmitters systems in the regulation of food intake. These studies support the need to better understand the role of the brain dopamine system in eating disorders as a means to develop effective therapeutic interventions.

DRUG STUDIES

^{18}FDG has been combined with other tracers to study drugs of abuse as well as therapeutic drugs to assess the overall effect on brain metabolism as well as its effects of on a specific cellular element (receptor, transporter or enzyme).

Cocaine

Cocaine is a powerfully addictive psychostimulant drug that binds to the dopamine, norepinephrine, and serotonin transporters.[43] There is mounting evidence that cocaine binding to the dopamine transporter produces a large, abrupt increase in synaptic dopamine. Because dopamine is a neurotransmitter involved in motivation and in reward and reinforcement, cocaine-induced elevations in dopamine produce an intense high, particularly when it is taken by the intravenously or smoked routes of administration.[44,45] To better understand the functional and neurochemical processes underlying the loss of control involved in cocaine addiction, PET studies in cocaine abusers and an age-matched comparison group have been performed with ^{18}FDG and with [^{18}F]N-methylspiroperidol to measure dopamine D2 receptor availability.[46] When compared with normal controls, cocaine abusers showed significant decreases in dopamine D2 receptor availability, which persisted 3 to 4 months after detoxification.[47] Decreases in dopamine D2 receptor availability were associated with decreased metabolism in several regions of the frontal lobes, most markedly orbital-frontal cortex and cingulate gyri. Dopamine dysregulation of these brain areas, which are involved in the channeling of drive and affect, has been postulated to lead to loss of control, resulting in compulsive drug-taking behavior. This early study formed the groundwork of construct explaining the loss of control in cocaine addiction based on the neuroanatomy of the meso-corticol-limbic dopamine system.[48] These multi-tracers PET studies in the same subjects suggest that the loss of control seen in the cocaine abuser may be grounded in deficits in this pathway. This is supported by evidence that frontal lobe deficits are associated with compulsive and repetitive behaviors, which bear a resemblance to the loss of control in the addicted subject who persists in taking the drug even when it is at great cost and is no longer pleasurable.

Methamphetamine

Methamphetamine is a potent, long-lasting stimulant that is closely related chemically to amphetamine and to ephedrine. Its pharmacological actions are thought to be mediated principally through its ability to release monoamines coupled to its ability to block reuptake. Methamphetamine has been reported to produce toxicity in monoaminergic neurons in laboratory animals.[49] After the observation that cocaine abusers have low dopamine D2 receptors, which are associated with reduced metabolism in frontal brain regions, a similar multi-tracer study was performed to determine whether methamphetamine abusers also have lower dopamine D2 receptors and whether there is an association between dopamine D2 receptor availability and glucose metabolism similar to that seen in the cocaine abuser.[50] Fifteen methamphetamine abusers and 20 nondrug-abusing comparison subjects were studied with [^{11}C]raclopride and ^{18}FDG to assess dopamine D2 receptors and brain glucose metabolism, respectively. Methamphetamine abusers had a significantly lower D2 receptor availability than comparison subjects. D2 receptor availability was associated with metabolic rate in the orbitofrontal cortex in abusers and in

comparison subjects. The association between level of dopamine D2 receptors and metabolism in the orbitofrontal cortex in methamphetamine abusers was similar to previous findings in cocaine abusers and suggests that D2 receptor-mediated dysregulation of the orbitofrontal cortex may be a common mechanism for loss of control and compulsive drug intake in addiction.[51]

^{18}FDG scans in the detoxified methamphetamine abusers also revealed higher metabolism in the parietal cortex and lower metabolism in the thalamus and striatum than for the comparison subjects.[52] Because the parietal cortex is a region devoid of any significant dopaminergic innervation, higher parietal metabolism in the methamphetamine abusers suggests effects on nondopaminergic circuits. In addition, the lower metabolism in the striatum and thalamus (major outputs of dopamine signals into the cortex) is likely to reflect the functional consequence of methamphetamine exposure to dopaminergic circuits. These results provide evidence that, in humans, methamphetamine abuse results in changes in function of dopamine- and nondopamine-innervated brain regions.

Tobacco Smoke

There are 45 million smokers and 400,000 tobacco-related deaths in the United State alone. Yet little is known about the mechanisms underlying the behavioral and epidemiological effects of tobacco smoke exposure and the success rate for smoking cessation treatments is limited. Tobacco (*Nicotiana tabacum*) contains several thousand chemical compounds, including nicotine, the major addictive component. However, PET imaging with the MAO B tracer [^{11}C]L-deprenyl-D2 showed that smokers have reduced levels of brain MAO B[53] and that this is not an effect of nicotine.[54] Because MAO B is involved in the breakdown of dopamine, which is implicated in reinforcement and motivating behaviors as well as movement, reduced MAO B may be one of the molecular mechanisms underlying some of the diverse behavioral and epidemiological effects of smoking.[55] To assess the specificity of the effect, brain glucose metabolism was also measured in these smokers using ^{18}FDG. Brain metabolism did not differ between groups for the global or for the brain regions examined nor was there any association between brain glucose metabolism and MAO B activity. This indicates that MAO B inhibition is a specific effect at least as it relates to the variables of blood flow and resting metabolism. As a follow-up to these PET studies, a MAO inhibitor was recently isolated from tobacco leaves[56] and the selective MAO B inhibitor, L-deprenyl has reported to be effective in smoking cessation.[57]

Methylphenidate

Methylphenidate (Ritalin) is an effective drug in the treatment of attention-deficit–hyperactivity disorder. It blocks the dopamine transporter, causing elevations in synaptic dopamine, which is one of the mechanisms by which it exerts its therapeutic effects.[58,59] However, the doses required therapeutically vary significantly between subjects and it is not understood what determines this variability. To identify the patterns of metabolic changes produced by intravenous methylphenidate and to examine whether an individual's baseline dopamine activity contributes to this pattern, brain glucose metabolism as measured with ^{18}FDG after two sequential doses of methylphenidate in 15 healthy subjects. Dopamine D2 receptor availability was measured with [^{11}C]raclopride to evaluate its relation to methylphenidate-induced changes in metabolism.[60] Methylphenidate produced variable changes in brain metabolism but it consistently increased metabolism in the cerebellum and reduced relative metabolism in the basal ganglia. The significant association between metabolic changes in the frontal and temporal cortices and in the cerebellum and D2 receptors suggests that methylphenidate's metabolic effects in these brain regions are due in part to dopamine changes and that differences in D2 receptors may be one of the mechanisms accounting for individual variability in response to methylphenidate.

Cholinergic Therapy

Acetylcholine mediates complex functions, such as attention, memory, and cognition, and clinical and postmortem studies suggest its involvement in the cognitive deterioration seen in Alzheimer's disease and in the memory loss associated with normal aging.[61] This has led to considerable effort to develop and evaluate drugs that enhance cholinergic activity. One of these is tetrahydroaminoacridine (tacrine), which enhances acetylcholine levels by inhibiting acetylcholinesterase. To assess the effect of tacrine on brain function and brain cho-

linergic function, three patients with Alzheimer's disease with moderate dementia were treated orally with the cholinesterase inhibitor tacrine (80 mg daily) for several months. PET scanning was performed before and after 3 weeks and 3 months of treatment with ^{18}FDG, S(-)- and R(+)-[^{11}C]nicotine (to measure nicotine binding sites) and [^{11}C]butanol (to measure brain blood flow).[62] Tacrine treatment increased the brain uptake of [^{11}C]nicotine. In all three patients, kinetic analysis indicated increased binding of (S)(-)-[^{11}C]nicotine in frontal and temporal cortices. Glucose metabolism was elevated after tacrine treatment for 3 months, and neuropsycological performance improved. Brain blood flow did not differ with tacrine treatment. A follow-up PET study with these three tracers was performed after 13 to 31 months of tacrine treatment.[63] Electroencephalogram and cognitive tests were also performed. Improvement of nicotinic receptors (measured as ^{11}C -nicotine binding), cerebral blood flow, electroencephalogram, and some cognitive and attentional tests occurred early after initiation of tacrine treatment compared with the glucose metabolism, which was increased after several months of tacrine treatment. The authors concluded that the functional effects of tacrine in Alzheimer patients appeared to be related to both dose and length of treatment and that intervention with tacrine in the early course of the disease might be necessary for clinical improvement.

SUMMARY

^{18}FDG is now available to most regions of the United States from a number of central production sites. Thus, it can be conveniently paired with other tracers in multi-tracer PET studies. This alleviates the burden of preparing both ^{18}FDG and more complex C-11- and F-18-labeled radiotracers in cases where staff or other resources are limiting. In this article, we have highlighted several examples from the literature showing the enhancement of information that is gained by pairing ^{18}FDG with other tracers in studies of the human brain during aging, neuropsychiatric disorders and in probing the functional consequences of drug treatment. Although the use of a functional tracer like ^{18}FDG is not as precise as the use of a radiotracer, which is more specific for a given neurotransmitter system, pairing ^{18}FDG with tracers that probe other neurochemical phenomena captures the best of both worlds.

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