Imaging Brain Cholinergic Activity with Positron Emission Tomography: Its Role in the Evaluation of Cholinergic Treatments in Alzheimer’s Dementia

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One of the strategies in the treatment of Alzheimer’s disease is the use of drugs that enhance cholinergic brain function, since it is believed that cholinergic dysfunction is one of the factors that contributes to cognitive deterioration. Positron emission tomography is a medical imaging method that can be used to measure the concentration, kinetics, and distribution of cholinergic-enhancing drugs directly in the human brain and assess the effects of the drugs at markers of cholinergic cell viability (vesicular transporters, acetylcholinesterase), at muscarinic and nicotinic receptors, at extracellular acetylcholine, at markers of brain function (glucose metabolism and blood flow), and on amyloid plaque burden in vivo in the brains of patients with Alzheimer’s disease. In addition, these measures can be applied to assess the drugs’ pharmacokinetic and pharmacodynamic properties in the human brain. Since the studies are done in living human subjects, positron emission tomography can evaluate the relationship between the drugs’ biological, behavioral, and cognitive effects; monitor changes in brain function in response to chronic treatment; and determine if pharmacologic interventions are neuroprotective. Moreover, because positron emission tomography has the potential to identify Alzheimer’s disease during early disease, it can be used to establish whether early interventions can prevent or delay further development. Biol Psychiatry 2001;49: 211–220 © 2001 Society of Biological Psychiatry

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Introduction

Acetylcholine is widely distributed within the human brain, where its physiologic functions are not well understood. Behavioral studies provide evidence that acetylcholine participates in 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 (Mihailescu and Drucker-Colin 2000). This has led to the use of drugs that enhance acetylcholine activity in the brain as treatments for AD.

Access to imaging technologies such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) and appropriate radiotracers makes it possible to evaluate noninvasively the acetylcholine system in the human brain. This review focuses on the use of PET to evaluate the acetylcholine system in the human brain and its use to evaluate drugs that enhance acetylcholine activity for the treatment of AD (acetylcholinesterase inhibitors, cholinergic agonists, and acetylcholine releasers). It should be noted that although we focus on cholinergic drugs, these are not the only treatments for AD, and similar strategies can be used to assess the effects of noncholinergic symptomatic or preventive treatments for AD (i.e., antioxidants, amyloid vaccine, estrogen replacement).

Positron emission tomography radiotracers are available that can be used to study various elements involved with cholinergic neurotransmission and function (Figure 1). These include:

- **Acetylcholine neuronal integrity.** Ligands have been developed to measure the acetylcholine vesicular transporter (transports acetylcholine from the cytoplasm to the vesicle) and acetylcholinesterase (enzyme that metabolizes acetylcholine).
- **Acetylcholine receptors.** Radioligands have been developed to measure both muscarinic and nicotinic receptors.
- **Brain function.** Tracers are available that enable measurement of regional brain glucose metabolism and cerebral blood flow (CBF), which can be used to assess activity of the regions modulated by acetylcholine.

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† Amyloid plaques and fibrillary tangles. Though plaques are not part of the cholinergic system, they are an integral part of brain pathology in AD and hence are of relevance in the evaluation of drug treatments for AD. Tracers have been developed to measure the concentration of amyloid in the brain.

† Transduction signaling. Cholinergic activity is likely to be regulated by intracellular signaling. Though there are PET radiotracers such as [11 C]arachidonic acid (Rapoport 2000) that permit evaluation of intracellular signal transduction processes, these have not been used to assess AD.

These radiotracers can be used with PET to investigate directly in the human brain a drug’s 1) pharmacokinetics and distribution and 2) mechanism(s) of action (pharmacodynamics). Because these studies are done in living patients, they can be used to determine the relationship between the neurochemical and cognitive/behavioral effects of the drug. So far very few PET studies have been done to assess the effects of drug treatment in AD. However, there are assumptions that, with the increase in PET centers and the greater availability of radiotracers, PET will become an important tool in the evaluation of new treatments in AD.

Imaging Strategies

Acetylcholine Neuronal Markers

Loss of acetylcholine cells is a characteristic feature of AD. Hence, radiotracers that serve as markers of acetylcholine neuronal integrity could be very useful for the evaluation of treatments in AD. In postmortem tissue, cholinergic cell loss is assessed by measuring the activity of choline acetyltransferase (ChAT), the enzyme that catalyzes the synthesis of acetylcholine. In patients with AD, postmortem studies have consistently documented a selective loss of cholinergic neurons in the basal forebrain (Coyle et al 1983) and a marked reduction in ChAT in the projection areas that correlate with dementia severity (Bierer et al 1995). Although there are no PET radiotracers for ChAT, there are radiotracers for acetylcholinesterase, or the acetylcholine vesicular transporter—the latter two having been shown to map acetylcholine cells in the brain and to have a good correspondence with ChAT (Mesulam and Geula 1992; Weihe et al 1996).

ACETYLCHOLINESTERASE. This is an enzyme that catalyzes the hydrolysis of acetylcholine to choline and acetic acid and is consistently reduced in the brain of AD patients. Though acetylcholinesterase is anchored in presynaptic membranes in the acetylcholine neuron as well as in postsynaptic membranes and in the intersynaptic space, it has a very good correspondence with ChAT. The activity of acetylcholinesterase can be measured with PET using labeled acetylcholine analogs that serve as substrates for acetylcholinesterase and hydrolyze to a hydrophilic product that is trapped in the cell (Kuhl et al 1999). Another method is to use radioligands that bind to acetylcholinesterase (Brown-Proctor et al 1999; Pappata et al 1996; Planas et al 1994).

The regional concentration of acetylcholinesterase in the human brain was first measured with PET using [11 C]physostigmine. In normal control subjects the pattern of distribution corresponded to that in the postmortem brain with a higher concentration in the striatum (> cerebellum > thalamus > cerebral cortex) (Pappata et al 1996). The activity of acetylcholinesterase has also been measured in AD patients and compared to that in control subjects using N-[11 C]-methylpiperidin-4-yl propionate ([11 C]PMP), which is a selective substrate for acetylcholinesterase with a 97% specificity (Kuhl et al 1999). Positron emission tomography studies showed no changes in acetylcholinesterase with normal aging and a reduction of 30% in patients with mild to moderate AD. The smaller reductions reported by this PET study as compared with the postmortem studies (90–95%) most likely reflect the fact that postmortem studies are mostly from patients with very advanced disease (Kuhl et al 1999).

Acetylcholinesterase inhibitors have been the most widely used drugs to treat AD. With PET it is now possible to assess the efficacy of these drugs in inhibiting acetylcholinesterase. For example, a PET study that used [11 C]PMP showed that acute treatment with physostigmine (1.5 mg administered intravenously over 60 min) markedly reduced acetylcholinesterase activity in the human brain (approximately 50%) (Kuhl et al 1999). These radioligands can be used to assess the efficacy of the
various acetylcholinesterase inhibitors that are used therapeutically and to determine the doses required to achieve optimal inhibition. They can also help identify patients in whom the concentration of acetylcholinesterase may be too low for acetylcholinesterase inhibitors to be effective.

**ACETYLCHOLINE VESICULAR TRANSPORTER.** These transporters are localized in the acetylcholine terminals and carry acetylcholine from the cytoplasm into the vesicles. Several radioligands that target the acetylcholine vesicular transporter have been labeled (Kuhl et al 1994; Mach et al 1997; Mulholland et al 1998). Of these, only (−)-5-[123I]iodobenzovesamicol ([123I]IBVM), a SPECT radiotracer, has been used to image the living human brain (Kuhl et al 1994). [123I]IBVM is an analog of vesamicol that binds to the acetylcholine vesicular transporter. The relative distributions of [123I]IBVM in the human brain correspond well with postmortem values reported for ChAT (Kuhl et al 1994). Cortical binding of [123I]IBVM in normal subjects declined only mildly with age (3.7% per decade), but it was markedly reduced in AD patients in whom the reductions predicted dementia severity (Kuhl et al 1996). The binding levels were also determined by the age of disease onset; patients with an age of onset of <65 years had reductions throughout the cortex and hippocampus (approximately 30%), whereas patients with an age of onset of >65 years had reductions only in the temporal cortex and hippocampus. This most likely reflects the greater cholinergic loss in early- rather than in late-onset AD (Rosser et al 1984).

There are currently no published studies utilizing acetylcholine vesicular transporters to assess the effects of pharmacologic treatments in AD. These tracers are likely to be particularly useful for assessing neuroprotective treatments and may be of use in the detection of early disease.

**Acetylcholine Receptors**

The actions of acetylcholine are mediated through nicotinic and muscarinic cholinergic receptors, which transduce signals via different mechanisms. The muscarinic receptors interact with G proteins, whereas the nicotine receptors are ligand-gated ion channels. These receptors are localized in both presynaptic and postsynaptic targets. From postmortem studies it appears that nicotinic receptors are markedly reduced in the brain of AD patients, whereas muscarinic receptors are much less affected (Nordberg and Winblad 1986). Drugs that target both nicotinic (Li et al 2000) and muscarinic receptors are being developed as potential treatments in AD (Bymaster et al 1998).

Desirable properties for PET or SPECT acetylcholine receptor radioligands are good kinetic properties, high specific-to-nonspecific binding ratios, good toxicologic profiles, and selectivity for receptors’ subtypes.

**MUSCARINIC RECEPTORS.** Several radiotracers have been developed for mapping muscarinic receptors (Dewey et al 1990; Eckelman et al 1984; Weinberger et al 1991; Zubieta et al 1998). In normal subjects, the regional distribution of these radiotracers in the brain corresponds to the pattern from postmortem studies that have high levels in the striatum, occipital cortex, and insular cortex, and low levels in the thalamus and cerebellum (Weinberger et al 1991). In accordance with postmortem findings, these imaging studies have shown a reduction in muscarinic receptors due to aging (Dewey et al 1990); studies in AD subjects have shown reductions as well as no changes in receptor levels (Wyper et al 1993). For the most part these radiotracers are limited by the lack of selectivity for the muscarinic receptor subtypes (M1–M4), except for [18F]3-(3-fluoropropylthio)-1,2,5-thiadiazol-4-yl)-1,2,5,6-tetrahydro-1-methylpyridine ([18F]FP-TZTP), which appears to bind predominantly to M2 receptors (Carson et al 1998).

The effects of treatment with the acetylcholinesterase inhibitor tacrine (80 mg daily) on muscarinic receptors was assessed in one AD patient using PET and [11C]benztropine. After 3 months of treatment, there was a decrease in the specific binding of [11C]benztropine, which was interpreted as a temporary downregulation of muscarinic receptors because at 10 months the reduction was no longer evident (Nordberg et al 1997). These radioligands may be particularly useful for determining the receptor occupancy by muscarinic agonists (Bymaster et al 1998).

**NICOTINIC RECEPTORS.** The first radioligand developed for nicotinic receptors was [11C]nicotine. The labeling of the two enantiomers of nicotine, (S)(−) and (R)(+), which predominantly bind to the low- and high-affinity nicotinic sites, respectively (Copeland et al 1991), allowed the separate assessment of nicotinic receptor subtypes (Nordberg et al 1991). However, the binding of these radiotracers is highly influenced by CBF and is limited by the brief drug receptor interaction time and its low specific-to-nonspecific binding ratio (Lundqvist et al 1998). Quantification of nicotinic receptors with [11C]nicotine requires a complex model that entails a separate assessment of CBF (Lundqvist et al 1998). Nicotine’s binding to nicotinic receptors is quite selective and is predominantly seen at the α4β2 nicotinic receptor subtype.

Several compounds with a higher affinity for the nicotinic receptor than that of nicotine have been labeled. Favored targets are analogs of epibatidine or derivatives of azetidine. Epibatidine has a high affinity and specificity...
for nicotinic receptors (20 times more potent than nicotine with little or no activity at other receptor types) (Ding et al 1996; Villemagne et al 1997). Positron emission tomography studies with \(^{18}\)F-labeled (\(t_{1/2} = 110\) min) analogs of epibatidine such as \([^{18}\text{F}]\)norchlorofluoroepibatidine (\([^{18}\text{F}]\)NFEP), \([\pm\text{-exo}-2-(2-[^{18}\text{F}]\text{fluoro-5-pyridyl})-7\text{-azabicyclo}[2.2.1]heptane (\([^{18}\text{F}]\)FPH), and \(\text{N}-\text{methyl}\) \([^{18}\text{F}]\)NFEP (\([^{18}\text{F}]\)N-methyl-NFEP) showed very high specific-to-nonspecific binding ratios in the nonhuman primate (Ding et al 1996, 1999; Villemagne et al 1997). Their highest binding occurred in the thalamus, where the binding was almost completely blocked by pretreatment with nicotine or cytisine, which confirms the specificity of the binding to this brain region. Unfortunately, epibatidine is very toxic, which may preclude its use in humans (Molina et al 1997). An epibatidine congener, 3-[(1-[\(^{11}\text{C}\)]methyl-2-(\(S\)-pyrrolidinyl)methoxy]pyridine (\(K_s = 150\) pm) shows a brain distribution similar to that of \([^{18}\text{F}]\)NFEP and may have a toxicologic profile that is better suited for human studies (Kassiu et al 1998). Several azetidine analogs have also been labeled. One of them, (\(S\))3-methyl-5-(1-[\(^{11}\text{C}\)]methyl-2-pyrrolidinyl)isoxazol (\([^{11}\text{C}]\)ABT-418), has been studied with PET and showed very fast uptake and clearance from the primate brain with no displacement by nicotine, indicating that it is unlikely to be suitable for PET studies. The azetidine analogs (\(R,S\))-1-\([^{11}\text{C}]\)methyl-2-(3-pyridyl)azetidine and 6-\([^{18}\text{F}]\)fluoro-3-(2-(\(\text{S}\)-azetidinylmethoxy)pyridine (\(K_s = 25–46\) pm) appear to have better kinetic properties and a higher specific-to-nonspecific binding ratio than \([^{11}\text{C}]\)ABT-418 and may potentially be good radioligands for human PET studies (Chefer et al 1999; Ding et al 2000a; Sihver et al 1999).

The only studies performed that measure nicotinic receptors in humans have been done with \([^{11}\text{C}]\)nicotine. Studies in AD patients have shown significant reductions in \([^{11}\text{C}]\)nicotine binding in the temporal and frontal cortices and in the hippocampus relative to control subjects. The changes in \([^{11}\text{C}]\)nicotine binding were associated with cognitive function and interpreted as reflecting reductions in nicotinic receptors in AD (Nordberg et al 1997). These studies also showed lower binding of the (\(R\))(+) enantiomer of nicotine relative to the (\(S\))(−) one in the AD brain, which was interpreted as reflecting a predominant loss of high affinity for nicotinic receptors.

The effects of tacrine (80 mg daily for 3 months) on nicotinic receptors was assessed in AD patients using \([^{11}\text{C}]\)nicotine (Nordberg et al 1997). Tacrine increased binding of \([^{11}\text{C}]\)nicotine in the temporal cortex of AD patients, which was interpreted as reflecting a restoration of nicotinic receptors. These results are in agreement with preclinical data showing that cholinergic stimulation leads to upregulation of nicotinic receptors (Svensson and Nordberg 1996). Tacrine also decreased the differences in the binding of the (\(R\))(+) enantiomer of nicotine relative to the (\(S\))(−) one, suggesting a preferential effect on high-affinity sites (Nordberg et al 1992).

Nicotinic receptor radioligands will also be useful in assessing the occupancy achieved by nicotinic agonists. There is also interest in the clinical use of allosteric nicotinic agonists such as galantamine, which facilitate cholinergic neurotransmission by binding to an allosteric site in the nicotinic receptor that is distinct from that of acetylcholine (Schrattenholz et al 1996). In this case the assessment of occupancy will require the use of a radiotracer that binds to this allosteric modulatory site.

**Extracellular Neurotransmitter Levels**

With PET or SPECT, it is now possible to measure changes in the extracellular concentration of neurotransmitters in the brain. This is done indirectly by measuring the binding of a radiolabeled compound that is in competition with the endogenous neurotransmitter for binding to its targeted receptor (Figure 2). The difference in the binding of the radiotracer between a baseline condition and its binding after a drug intervention reflects the drug-induced changes in extracellular neurotransmitter concentration. Applications of this strategy have been limited by the lack of appropriate radiotracers. In the case of acetylcholine this can be achieved with \([^{18}\text{F}]\)NFEP, since this ligand has very good test–retest reproducibility and is sensitive to competition with endogenous acetylcholine (Ding et al 2000). Because of the toxicity of \([^{18}\text{F}]\)NFEP, these studies have been limited to nonhuman primates and have shown that the acetylcholinesterase inhibitor physostigmine (0.03 mg/kg intravenously) significantly increases synaptic acetylcholine concentration in the striatum (Ding et al 2000). Note that this dose of physostigmine is not very different from that which induced a 50% inhibition of acetylcholinesterase in the human brain (1.5 mg in a 75-kg person) (Kuhl et al 1999). Positron emission tomography studies in primates also indicate that the M2 receptor radioligand FP-TZTP may be sensitive to competition with endogenous acetylcholine because its binding was also inhibited by physostigmine (Carson et al 1998). The measure of extracellular acetylcholine is particularly promising for the evaluation of pharmacologic treatments, since most drugs are targeted to enhance cholinergic function by increasing extracellular acetylcholine.

Although the drugs targeted for AD focus on acetylcholine, their secondary effects on other neurotransmitters may be of relevance for treatment (i.e., glutamate, serotonin, dopamine). Positron emission tomography could in principle be used to assess the effects of cholinergic drugs
in release of these neurotransmitters and to assess their contribution to treatment. Currently, dopamine is the only neurotransmitter other than acetylcholine for which there is a PET radioligand, [11 C]raclopride, and a SPECT radioligand, [(123)I]iodobenzamide. Both are sensitive to changes in endogenous concentration of the neurotransmitter (Dewey et al 1993; Laruelle et al 1997; Volkow et al 1994).

**Brain Metabolism and Cerebral Blood Flow**

Brain metabolism, which can be measured with PET ([18 F]2-deoxy-D-glucose or [11 C]2-deoxy-D-glucose), and CBF, which can be measured with PET using [15 O]water or [11 C]butanol or with SPECT using technetium 99m-labeled D,L-hexamethyl-propylene amine oxime or N-isopropyl-p-[123 I]iodoamphetamine (Devous 1995), serve as markers of brain function.

The studies of brain glucose metabolism in AD were started 20 years ago (Farkas et al 1982) and revealed marked reductions in brain glucose metabolism that were most accentuated in advanced AD. The metabolic and CBF decrements are most severe in association cortices (parietal, temporal), with relative sparing of primary sensory and motor cortices, basal ganglia, and cerebellum (Herholz et al 1999; Holman et al 1992). These metabolic changes are evident before clinical diagnosis (Perani 2000) and predict clinical deterioration (Herholz et al 1999), providing evidence of their usefulness for early AD detection. It is outside of the scope of this article to review the literature on PET imaging in early AD detection, and several excellent reviews have been written on this subject (Fox and Rossor 1999; Small 1996).

Brain metabolism and CBF in AD patients have also been measured during cognitive, sensory, and/or pharmacologic stimulation. Stimulation studies can detect abnormalities in brain regions from AD patients that, at rest, do not differ from those of control subjects. For example, metabolism in the visual and auditory cortices predicts dementia severity in AD patients only when subjects are tested during audiovisual stimulation, not when they are tested at rest (Pietrini et al 1999).

Measures of metabolism and CBF can be used to assess the functional effects of drugs in the human brain. Most of the PET studies have assessed the effects of drugs during resting and during cognitive or somatosensory stimulation. Under resting conditions acute cholinergic stimulation with physostigmine does not affect CBF in healthy control subjects but it increases CBF in the most affected regions in AD patients (Geaney et al 1990; Gustafson et al 1987). Increases in CBF in AD patients have also been reported after acute and fairly short periods of treatment with cholinesterase inhibitors such as tacrine and v仑acrine, and with the acetylcholine releaser linopirdine (van Dyck et al 1997). Similarly, SPECT studies have shown increases in CBF after treatment with the cholinesterase inhibitor donepezil (Staff et al 2000; Warren et al 1998). Increases in brain metabolism have been reported after long periods of treatment with cholinergic-enhancing drugs (Nordberg 1999) but not after short periods (Szelies et al 1986).

Studies assessing the effects of cholinergic stimulation during cognitive stimulation can map the effects of drugs on the brain regions involved in the response to the cognitive task. For example, in healthy control subjects given physostigmine, the drug-induced improvement in performance on a working memory task was correlated with drug-induced decrements in CBF in the right midfrontal gyrus, which is a region involved with working memory (Furey et al 1997). These results suggest that enhancement of cholinergic function can improve processing efficiency. Studies have started to assess the effects of
cholinergic-enhancing drugs on activation responses during memory stimulation in AD.

Amyloid Plaques

Confirmation of the clinical diagnosis of AD is based on the detection of amyloid plaques and neurofibrillary tangles in the brain. Unfortunately, such measures, until recently, could only be done postmortem. However, recent developments in radiotracers may now allow for the measurement of amyloid plaques and neurofibrillary tangles in the brain in vivo. Several strategies have been proposed for use with PET (Barrio et al 1999) or SPECT (Bornebroek et al 1996; Zhen et al 1999) that are based on labeling analogs of Congo Red, a dye that is used to stain amyloid in postmortem tissue.

Positron emission tomography studies with 2-(I-6-[2-[18F]fluoroethyl)-(methyl)-amino]-2-naphthyl)ethylene) malononitrile ([18F]FDDNP) have shown good uptake in the human brain and greater accumulation and slower clearance of [18F]FDDNP in AD patients than in control subjects. The accumulation in AD patients was greater in the hippocampal region and was detected even in patients with mild AD. The areas with high [18F]FDDNP retention were the ones with low glucose metabolism (Barrio et al 1999). The binding of [18F]FDDNP to amyloid plaques was confirmed in postmortem studies.

These radiotracers will be of use not only in diagnosis of AD but also in the investigation of the temporal relationship between amyloid deposition, neuronal loss, and cognitive decline and assessment of the effects of drugs in disease progression. Also, these radiotracers may provide treatment for AD patients early in their disease when response to treatment is usually better.

Imaging Drug Effects

Pharmacokinetics and Distribution in the Brain

Drugs can be labeled with positron emitters without changing their pharmacologic properties. This allows for the investigation of their regional distribution and pharmacokinetics in the human brain. Acetylcholine-enhancing drugs that have been labeled with positron emitters include nicotine, tacrine, and physostigmine.

Studies using [11C]nicotine showed that its highest uptake occurred in the cortex, thalamus, and striatum (Halldin et al 1992; Nordberg et al 1989). This pattern was poorly altered by unlabeled nicotine, which indicates that only a small portion of [11C]nicotine binding is specific. The largest reductions in [11C]nicotine binding in subjects treated with unlabeled nicotine occurred in the thalamus (30% decrease) (Muzic et al 1998), which is one of the brain regions with the highest density of α4β2 nicotinic receptors (Marubio et al 1999). After intravenous administration, [11C]nicotine enters the human brain very rapidly, achieving peak concentrations between 2–4 min after its administration. The half-life of [11C]nicotine in the brain, when administered with pharmacologic doses of nicotine, ranged between 22 min (thalamus) and 36 min (temporal cortex) (Hara and Kosaka 1995). This fast pattern of pharmacokinetics corresponds well with the rapid temporal course of its pharmacologic effects in humans and is likely to account for, in part, the high frequency at which cigarettes are smoked.

The cerebral distribution of tacrine in the human brain was studied using [11C]tacrine and showed higher uptake in gray (putamen > cerebellum > thalamus) than in white matter. [11C]Tacrine’s distribution did not correspond to the regional concentrations of acetylcholinesterase in the human brain, which most likely reflects its high levels of nonspecific binding (Traykov et al 1999). After intravenous administration, [11C]tacrine reached its maximum uptake in the brain between 10 and 40 min and had a half-life that varied from 2.44 hours in the thalamus to 3.42 hours in the cerebral cortex. The brain kinetics of [11C]tacrine are consistent with the plasma pharmacokinetics of tacrine in AD patients.

The regional distribution of [11C]physostigmine in the human brain showed that its initial distribution mainly reflects CBF. However, the distribution at 25 min corresponded well to the regional activity of acetylcholinesterase, with highest concentration in the striatum and relatively low concentrations in the cerebral cortex (Pappata et al 1996). After intravenous administration, [11C]physostigmine was rapidly taken up in the brain and peaked within a few minutes. It had a half-life that varied from 35 min in the striatum to 20 min in the cerebral cortex (Pappata et al 1996). The pharmacokinetics of this drug in the brain correspond well with the temporal course for its cognitive effects.

Pharmacodynamics

The mechanism of action of a drug can be tested with PET using radiotracers that measure the putative pharmacologic effects of the drug. This includes the assessment of its primary molecular target(s) as well as secondary effects (Figure 1).

Studies that have been done to assess the effects of the drug at its molecular target show the relationship between doses of a drug and percent occupancy of receptors or transporters, or percent of enzyme inhibition. This can be done either by using the radiolabeled drug itself, if it has a good specific-to-nonspecific binding ratio, or by using a radioligand that binds to the same site as the drug. For example, the relationship between nicotine doses and
nicotinic receptor occupancies was investigated using \( ^{18}F \)NFEP (Ding et al 2000b). The study, which was done in nonhuman primates, showed that nicotine doses of 0.005, 0.01, 0.02, and 0.04 mg/kg resulted in receptor occupancies of 40%, 45%, 48%, and 58%, respectively. The plasma nicotine concentrations achieved were equivalent to those seen in humans after smoking a cigarette (41 ng/mL for a cigarette that contains 1.9 mg nicotine), indicating that approximately 40% of the nicotine receptors are occupied after a cigarette has been smoked (Ding et al, in press) (Figure 3). This same strategy can be applied to measure the receptor occupancies achieved by nicotinic or muscarinic drugs at doses that improve cognitive or behavioral function. Equivalent studies can also be done to assess the efficacy of cholinesterase inhibitors in inhibiting acetylcholinesterase.

In addition, PET can be used to evaluate secondary effects, which may ultimately be responsible for the therapeutic effects of the drug. These secondary effects may occur after either acute or chronic drug administration. In the case of acetylcholinesterase inhibitors, this could include the assessment of extracellular acetylcholine concentration, extracellular concentration of other relevant neurotransmitters, nicotinic and muscarinic receptors, and brain function (brain glucose metabolism or CBF). Moreover, because of the low dosimetry of positron emitters, studies can be done that use multiple tracers to evaluate more than one pharmacologic effect at different points in time. For example, the effects of treatment with tacrine (80 mg day) in AD patients on nicotinic receptors, brain glucose metabolism, and CBF were evaluated before and after 3 weeks and 3 months of treatment (Nordberg et al 1992). The study showed that tacrine increased the levels of nicotinic receptors and increased brain glucose metabolism, but it did not change CBF. Though previous studies failed to document changes in metabolism with cholinergic-enhancing drugs, this most likely reflects the much longer treatment duration of this study (Nordberg et al 1992). The relevance of treatment duration in the effects of tacrine on brain metabolism was recently demonstrated by a study showing that, though the effects of tacrine on nicotine receptors occurred early in the course of treatment (3 weeks), those in metabolism were observed only after months of treatment (Nordberg et al 1998).

Summary

Positron emission tomography has an important role in the investigation of treatments for AD during early stages of drug development and during the later stages of clinical use. At early stages PET is able to provide information that helps to determine optimal dosing regimes and to understand the drug’s mechanism(s) of action. At later stages PET can be used to monitor the effects of drug treatment. Once the drug has been approved, PET can still play a role by helping to identify individuals who are most likely to respond to treatment.

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