Positron Emission Tomography and Single-Photon Emission Computed Tomography in Substance Abuse Research

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Many advances in the conceptualization of addiction as a disease of the brain have come from the application of imaging technologies directly in the human drug abuser. New knowledge has been driven by advances in radiotracer design and chemistry and positron emission tomography (PET) and single-photon emission computed tomography (SPECT) instrumentation and the integration of these scientific tools with the tools of biochemistry, pharmacology, and medicine. This topic cuts across the medical specialties of neurology, psychiatry, oncology, and cardiology because of the high medical, social, and economic toll that drugs of abuse, including the legal drugs, cigarettes and alcohol, take on society. This article highlights recent advances in the use of PET and SPECT imaging to measure the pharmacokinetic and pharmacodynamic effects of drugs of abuse on the human brain.

In spite of the massive public health problem associated with drug abuse, there are no completely effective treatments. This is partly due to a relatively poor understanding of the neurochemical changes that drugs of abuse produce on the human brain and the relationship of these changes to their behavioral and addictive properties. With the development of modern imaging technologies and a variety of labeled drugs and radiotracers, it has now become possible to visualize and quantify many aspects of drug pharmacokinetics and pharmacodynamics directly in the human brain and to relate these parameters to the behavioral and toxic properties of drugs (reviewed by Fowler and Volkow[1]). This topic cuts across the medical specialties of neurology, psychiatry, oncology, and cardiology because of the high medical, social, and economic toll that drugs of abuse; including especially the legal drugs, cigarettes and alcohol, take on society.

In this article we will highlight recent applications of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging to major drugs of abuse-cocaine, methamphetamine, methylenedioxymethamphetamine (MDMA), alcohol, opiates, tobacco, marijuana, and inhalants. We have focused on human studies and we will begin with a brief discussion of the brain dopamine system that is at the heart of the reward system in the human brain. We will conclude with a brief discussion on vulnerability and addiction treatment. We note that there is increasing trend to use combinations of different radiotracers and different imaging modalities along with behavioral and drug challenge strategies to understand the relationship between pharmacological and functional factors and addictive behaviors.

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THE BRAIN DOPAMINE SYSTEM

The brain dopamine system is central to the brain's reward system and a major molecular target in the investigation of drugs of abuse.[2] Briefly, the cell bodies which produce dopamine are located in the substantia nigra and the ventral tegmental area in the midbrain and project to the striatal area that includes what has come to be known as the reward center, the nucleus accumbens. Dopamine cells from the midbrain also project to various cortical and limbic brain regions. The association of dopamine and reward and reinforcement stems from the observation that all drugs of abuse elevate dopamine in the nucleus accumbens.[3] Typically, drug induced elevations in dopamine occur rapidly after the administration of the drug and are associated with an intense euphoria ("high"). Though different drugs of abuse act by different mechanisms, elevated synaptic dopamine is common to all of them.

The study of substance abuse using PET and SPECT has advanced because of the availability of a variety of radiotracers which have specificity for different cellular elements of the brain dopamine and other neurotransmitter systems. These include receptors, transporters, vesicular storage sites, pre-

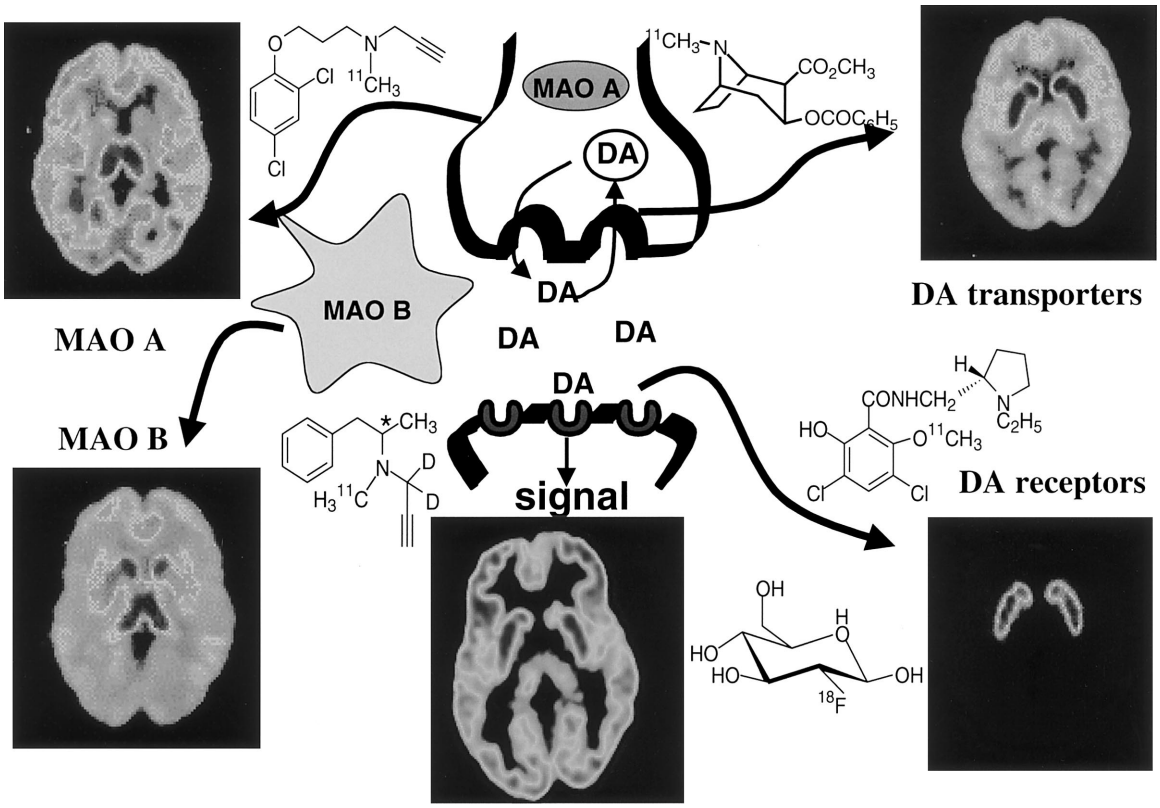

Fig 1. Diagram depicting the dopamine nerve terminal showing radiotracers and parametric images for the dopamine transporter (with [^{11}C]cocaine), dopamine receptors (with [^{11}C]raclopride), glucose metabolism (with ^{18}FDG) and monoamine oxidase (MAO) A and B (with [^{11}C]clorgyline and [^{11}C]L-deprenyl-D2).

cursors and enzymes Fig 1.[4] PET and SPECT have also been used to assess the effects of psychostimulant and other challenges on synaptic dopamine using dopamine receptor ligands that are sensitive to the endogenous concentration of dopamine, and to drug-induced changes in brain function with radiotracers for measuring blood flow and glucose metabolism. Finally, the use of the labeled drug itself provides unique information on its pharmacokinetics in the brain and in peripheral organs. Although dopamine is a central neurotransmitter in the study of addiction, other neurotransmitters also play a role and the interactions of different neurotransmitters is a key issue in normal and disease states.

COCAINE

(−)-Cocaine is a powerfully addictive psychostimulant drug isolated from erythroxylon coca. It binds to dopamine, norepinephrine, and serotonin transporters with micromolar to submicromolar affinity.[5] Cocaine's behavioral properties have been generally attributed to its ability to block the dopamine transporter (DAT) located on the presynaptic terminal. The DAT removes dopamine from the synapse and, therefore, terminates its action. DAT blockade results in the elevation of synaptic dopamine (DA) in the nucleus accumbens and the ensuing stimulation of dopamine receptors. The highest density of binding sites for cocaine is in the basal ganglia, the brain region containing the highest density of dopamine terminals, with minimal binding in other brain regions (reviewed Fowler et al[6]). Cocaine also is a potent local anesthetic[7] and has vasoactive properties.

The earliest use of imaging to study cocaine abuse reported large focal decreases in cerebral blood flow in heavy cocaine users probably reflecting cocaine's vasoconstrictive properties.[8] Blood flow decrements were measured with $H_2{}^{15}O$ and PET and these observations were later confirmed with SPECT and ^{99m}Tc-HMPAO and [^{123}I]iodoamphetamine.[9,10] At about the same time, brain dopamine metabolism as assessed by [^{18}F]fluoro-

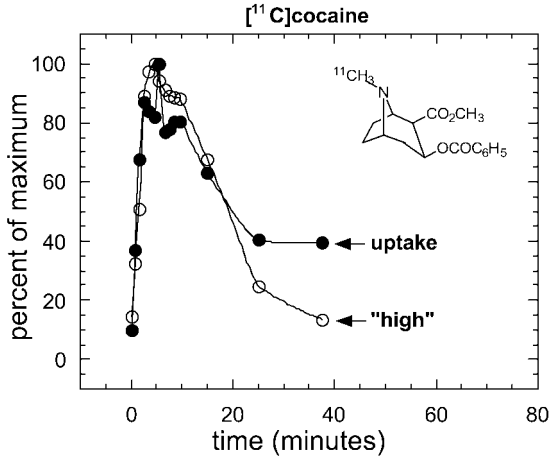

Fig 2. Time course of [^{11}C]cocaine in the brain along with the time course of the "high".[12,13]

DOPA, was reported to be reduced in the brains of cocaine abusers.[11]

Smoked and intravenously administered cocaine produces a rapid and intense "high" that rapidly subsides after administration. [^{11}C]Cocaine was developed to investigate the relationship between the "high" and the presence of cocaine in the brain (reviewed by Fowler et al[6]). The first studies of cocaine pharmacokinetics were carried out at tracer doses of [^{11}C]cocaine and showed binding to DATs in human basal ganglia. The absolute brain uptake was high and rapid (8-10% injected dose peaking 4-6 minutes after injection) and followed by a rapid clearance (half-life 20 minutes).[12] This study and a later study in current cocaine abusers using behaviorally active doses of cocaine provided the first evidence of a parallelism between the kinetics of uptake and clearance of cocaine in the brain and time course of the cocaine-induced "high".[13] Though the important link between the rate of drug delivery to the brain and reinforcement has been known for many years,[14] this study was the first to corroborate the parallel between rapid brain uptake and reinforcement in humans Fig 2.

While cocaine's rapid pharmacokinetics and high brain uptake are obviously important variables in producing its intense behavioral effects, a knowledge of the degree to which cocaine occupies the DAT at behaviorally active doses is also of intrinsic importance and also provides an important baseline when assessing the abuse liability of drugs including therapeutic drugs. Using [^{11}C]cocaine as a tracer for DAT occupancy, it was determined that DAT occupancy in excess of 60% is required in order for a "high" to be perceived from the intravenous administration of cocaine.[13,15] A later study compared DAT occupancy with different routes of administration (intra-nasal vs, intravenous vs smoked cocaine) in cocaine abusers while also measuring the subjective effects.[16] Even though the intensity and the time course of the behavioral response was significantly different for the three routes of administration, there was no significant difference in DAT occupancy (all were $>$60%). The onset of the "high" was the most rapid with the smoked $>$intravenous$\gg$ intranasal consistent with prior studies. This was the first evidence in humans that differences in the reinforcing effects of cocaine as a function of the route of administration are not due to differences in the degree of occupancy of the DAT. Moreover, more rapid onset of the subjective effects for smoked and intravenous vs intranasal cocaine highlights the importance of the rate of cocaine's delivery into the brain.

In spite of the complexity of cocaine's interactions with tissue, there is mounting evidence that the binding of cocaine to the DAT with its rapid ensuing elevation of dopamine dominates its behavioral effects in humans. The first human study designed to quantitatively assess the relationship between drug-induced increases in brain dopamine and the reinforcing effects of psychostimulant drugs in humans used a challenge dose of intravenous methylphenidate (a drug that, like cocaine, blocks the DAT) and [^{11}C]raclopride (which is sensitive to drug-induced changes in dopamine). It showed that the stimulant-induced 'high' is associated with increases in brain dopamine and that there is a quantitative relationship between levels of D2 receptor occupancy by dopamine and the intensity of the high Fig 3.

While the measurement of DAT occupancy and cocaine kinetics have provided an important perspective on the factors contributing to the intense behavioral effects of the drug, PET studies of the cocaine abuser at baseline have provided important information on the brain circuits that underlie the loss of control characterizing the cocaine addicted individual. Here, PET studies have consistently shown long lasting decreases in dopamine D2 receptors in cocaine abusers when compared with controls.[18,19] Cocaine abusers also showed significant reductions in DA release in response to a

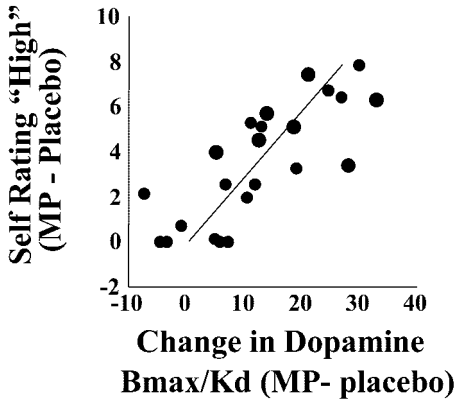

Fig 3. Relationship between the intensity of the "high" and the change in synaptic dopamine levels after a challenge dose of methylphenidate.[17]

stimulant challenge when compared to a control group.[19] This led to the suggestion that decreases in dopamine D2 receptors coupled with the decreases in dopamine release could result in an understimulation of reward circuits which could put subjects at greater risk for seeking drug stimulation as a means to compensate for this deficit and to temporarily activate these reward circuits.

Support for this hypothesis came from PET studies of brain glucose metabolism in cocaine abusers during short and long term withdrawal[20,21] and included a group of subjects in whom both dopamine D2 receptors and glucose metabolism were measured using [^{18}F]N-methylspiroperidol and ^{18}F-2-fluoro-2-deoxy-D-glucose(^{18}FDG) respectively.[22] Reductions in dopamine D2 receptors were associated with decreased activity in anterior cingulate gyrus (CG) and orbitofrontal cortex (OFC) which are both projection areas of the mesolimbic dopamine system (Fig 4). The involvement of these two brain regions in addictive behaviors could result from their role in motivation and drive and in their inhibitory control over emotional responses. It is important to note that the OFC is known to be involved in compulsive behavior.[23] Therefore, the disruption of the CG and the OFC could result in an inability to control the intake of the drug under emotionally stressful situations.[24]

Besides the brain dopamine system, the endogenous opioid system and the brain serotonin system have also been implicated in cocaine dependence and craving. Brain mu opioid binding was increased in cocaine addicts studied 1-4 days after their last use of cocaine using PET and [^{11}C]carfentanyl. Increased binding was positively correlated with the severity of cocaine craving.[25] A recent study examining the role of the brain serotonin system in cocaine-dependent subjects during acute abstinence using [^{123}I]β-CIT and a comparison group of non-abusing control subjects suggested serotonergic dysfunction during acute cocaine abstinence.[26]

Cocaine's effects on monoamine concentration in the brain may be mirrored in its effects on monoamine concentration and regulation in the peripheral organs. The short term distribution of [^{11}C]cocaine and its labeled metabolites (at tracer doses) was measured in peripheral organs in 14 healthy male subjects.[27] The rate of uptake and clearance varied with different organs. Peak uptake occurred in heart and kidneys at 2-3 minutes, in the adrenals at 7-9 minutes and in the liver at 10-15 minutes. There was no uptake in the lungs. Although no assessment of the chemical form or binding specificity was made in these studies, the radioactivity in organs with peak uptake at early times (heart, adrenals, and kidneys) probably is in the chemical form of cocaine itself while that which slowly accumulates probably reflects labeled metabolites of cocaine.

The high uptake of cocaine in the human heart is of potential medical importance because cardiotoxicity is a major medical complication in cocaine abuse.[28] Cocaine has been shown to inhibit the norepinephrine transporter in the baboon heart using 6-[^{18}F]fluoronorepinephrine[29] and in the hu-

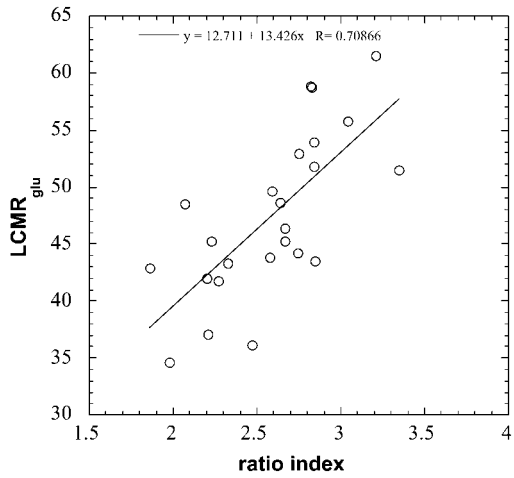

Fig 4. Relationship between glucose metabolic rate in the OFC (units are μmol/100g/min) and dopamine D2 receptor availability as measured by the ratio index.[22]

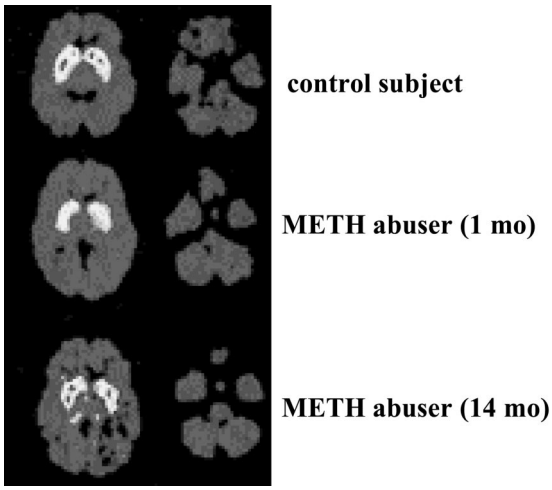

Fig 5. Parameteric images of dopamine transporter availability in a control subject and a methamphetamine abuser 1 month and 14 months after last use of methamphetamine.[34]

man cocaine abuser using [^{11}C]hydroxyephedrine.[30] This may account for some of the reports of cocaine-induced cardiotoxicity in athletes who use cocaine. Exercise would cause a release of norepinephrine which stimulates the adrenergic system. In the normal healthy individual, this would be regulated through the norepinephrine transporter whereas in the cocaine user, this protective mechanism would be disabled.

METHAMPHETAMINE

Methamphetamine is closely related both chemically and pharmacologically to amphetamine and to ephedrine. Its pharmacological actions are thought to be mediated principally through its ability to release monoamines coupled to its reuptake properties. It has a strong long-lasting stimulant response and has been reported to produce toxicity in monoaminergic neurons in laboratory animals.[31]

Recent neuroimaging studies have investigated the effects of chronic methamphetamine abuse on the brain dopamine system in methamphetamine abusers and have documented significant losses in DAT in vivo using [^{11}C]WIN 35428[32] and [^{11}C]d-threo-methylphenidate.[33] Losses in DAT in methamphetamine abusers are associated with reduced motor speed and impaired verbal learning.[33] In a study by Volkow et al[34] some of the methamphetamine abusers were also studied after a prolonged (12-17 months) abstinence. DAT recovered significantly (Fig 5) though there was not a complete recovery of neuropsychological function. These findings have treatment implications because they suggest that protracted abstinence may reverse some of methamphetamine-induced alterations in brain dopamine terminals. Another PET study in male methamphetamine abusers showed that longer use of methamphetamine is associated with greater reduction in DAT and more severe psychiatric symptoms and that DAT reduction is long-lasting even if methamphetamine use ceases.[35]

Dopamine D2 receptors and brain glucose metabolism were also measured in the same group of methamphetamine abusers in whom DAT were measured using [^{11}C]raclopride and ^{18}FDG.[36] Consistent with other addictions (cocaine, heroin, alcohol), methamphetamine abusers had a significantly lower level of dopamine D2 receptor availability than comparison subjects. Moreover, D2 receptor availability was associated with metabolic rate in the orbitofrontal cortex consistent with the hypothesis that dopamine D2 receptor-mediated dysregulation of the orbitofrontal cortex could underlie a common mechanism for loss of control and compulsive drug intake in drug addiction.[24]

Although most studies have focused on the effect of chronic methamphetamine abuse on the

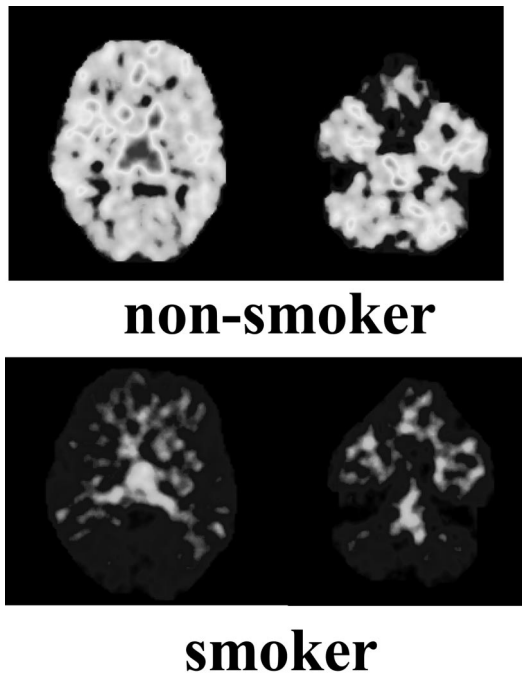

Fig 6. Parametric images of brain MAO B in a non-smoker and in a smoker.[76]

dopamine, there is evidence that regions other than those innervated by DA cells are also affected. In a PET study with ^{18}FDG, 15 detoxified methamphetamine abusers and 21 comparison subjects were compared.[37] Whole brain metabolism in the methamphetamine abusers was 14% higher than that of control with differences most prominent in the parietal cortex (+20%), a region devoid of DA innervation. This study provides evidence that, in humans, methamphetamine abuse results in changes in the function of both dopamine and non dopamine-innervated brain regions.

METHYLENEDIOXYMETHAMPHETAMINE (MDMA)

MDMA is currently a popular recreational drug that potently releases dopamine and serotonin from vesicular storage sites.[38] Its escalating use as a club drug has raised concerns because of evidence that it is toxic to serotonin neurons in laboratory animals.[39,40] Due to its increased use and the potential for neurotoxicity, PET, and SPECT have been directed to understanding its effects on the human brain, particularly its potential for damaging serotonergic neurons. The first neuroimaging study in MDMA users who were currently abstaining from use showed a decrease in serotonin transporter availability using [^{11}C]McN5652.[41] In a recent SPECT study, [^{123}I]β-CIT was used to measure serotonin transporter density in normal controls, in MDMA users, and in ex-MDMA users who had been abstinent for more than 1 year. Results from this study indicated that heavy use of MDMA was associated with neurotoxic effects on serotonin neurons, that women may be more susceptible than men, and that MDMA-induced changes in several brain regions of female ex-MDMA users are reversible.[42]

PET and ^{18}FDG studies of the relationship between ecstasy use and long-lasting alterations in brain glucose metabolism in 93 ecstasy users and 27 subjects without any known history of illicit drug abuse revealed that MDMA users have long-lasting changes in normalized brain glucose metabolism with lower uptake in striatum and amygdala relative to controls. In addition ^{18}FDG uptake was significantly more affected in the case of very early abuse.[43]

The cerebrovasculature is regulated in part by the serotonergic system raising questions of whether chronic use of MDMA could produce alterations in cerebral blood flow through its actions on the brain serotonin system. SPECT (with ^{133}Xe and with ^{99m}Tc-HMPAO) was used to evaluate 21 abstinent recreational MDMA users and 21 age- and gender-matched healthy subjects.[44] Ten of the MDMA subjects also had repeat SPECT and MRI after receiving two doses of MDMA. This study showed that low-dose recreational MDMA use does not cause detectable persistent rCBF changes in humans suggesting that either that serotoninergic deficits do not affect rCBF or that the damaged serotonergic terminals regenerate.

ALCOHOL AND ALCOHOLISM

The neurochemical mechanisms by which alcohol produces its psychoactive effects as well as the changes in the brain that accompany chronic alcohol abuse are not well understood. A number of imaging studies have shown that acute alcohol administration decreases brain glucose metabolism and increases cerebral blood flow (reviewed by Fowler et al[6]). Moreover, alcoholics showed a larger metabolic response to acute alcohol administration in spite of the fact that they showed a reduced subjective response to the intoxicating properties of alcohol.[45] This mismatch between metabolic and behavioral responsivity in alcoholics could reflect tolerance of the brain to alcohol-induced metabolic changes. Most studies of alcoholics without neurological impairment have documented abnormalities in frontal metabolism, a finding that is consistent with non-PET studies measuring regional cerebral blood flow.[46] Interestingly, decrements in brain glucose metabolism have been reported to partially recover in alcoholics, particularly during the first 16-30 days after withdrawal.[47]

Because both alcohol and benzodiazepines drugs each have a binding site on the GABA-benzodiazepine receptor (GABA-BZR) complex, it has been postulated that some of the neurochemical effects of alcohol are mediated through this pathway. To test the involvement of the GABA-BZR on the effects of alcohol, the effects of an acute challenge with a benzodiazepine drug on brain metabolism has been evaluated (reviewed by Volkow et al[4]). Similar to alcohol, benzodiazepines decreased brain glucose metabolism. Alcoholics and comparison subjects also responded differently. Comparison subjects and alcoholic subjects showed a similar response to lorazepam in

occipital and cerebellar metabolism, but the alcoholics showed a blunted response in thalamus, basal ganglia, and orbitofrontal cortex.[48] This could reflect the effect of either chronic alcohol administration and/or withdrawal. Genetic differences could also come into play because nonalcoholic subjects with a family history positive for alcoholism (FHP) showed lower baseline cerebellar metabolism than FHN when challenged with lorazepam. FHP subjects also showed a blunted response in the cerebellum. This correlated with motor impairment and could account for the decreased sensitivity to the motor effects of alcohol and benzodiazepines in FHP subjects.[49]

The effects of an acute challenge with alcohol has been measured with ^{18}FDG and PET and produced decreases in occipital cortex and increases in left temporal cortex similar to previous studies with lorazepam in healthy normal subjects.[50] This provides additional evidence for similarities between the pharmacological effects of alcohol and benzodiazepine drugs.

Neuroimaging has also been used to study alcohol toxicity.[51] Building on evidence that alcohol has effects on the GABA-BZR, PET imaging have shown decreased benzodiazepine receptor levels in alcoholics with [^{11}C]flumazenil[52] that was also confirmed with SPECT and [^{123}I]iomazenil.[53] The authors suggest this might indicate either a toxic effect of alcohol on benzodiazepine receptors or a vulnerability factor for developing alcoholism. Though cortical atrophy occurs frequently in alcoholics and could be a confounding factor, another recent study reported that abstinent alcohol-dependent subjects had decreased levels of GABA-BZR even in regions in which gray matter atrophy was absent.[54]

Though there is considerable evidence of frontal lobe pathology in alcoholism, it is important to consider that the frontal lobe has heavy connections to different cortical and subcortical areas of the brain implicating specific neurotransmitter systems innervating the cortex. Supporting this are PET studies showing decreased DA D2 receptor availability in alcoholics.[55] Because D2 receptors in striatum are mainly localized in GABA cells these results provide supporting evidence of GABAergic involvement in the dopaminergic abnormalities seen in alcoholics.

In another study, SPECT and [^{123}I]PE2I and [^{123}I]epidepride were used to examine striatal and extrastriatal DA D2 receptors as well as DAT in late onset alcoholics.[56] Striatal presynaptic DAT densities (but not extrastriatal D2-receptor levels) were decreased among type 1 alcoholics relative to a healthy comparison group. SPECT and [^{123}I]IBZM studies also suggested a relationship between low striatal dopamine D2 receptor levels and vulnerability to early relapse in detoxified alcoholic patients.[57] In a study specifically examining changes in DA function during alcohol withdrawal with [^{123}I]β-CIT, alcoholics showed markedly lower DAT relative to healthy volunteers. DAT recovered to normal levels after abstinence.[58] The authors speculate that prolonged heavy drinking decreases DAT which may sensitize alcoholics to DA transmission and may lead to early relapse after ethanol withdrawal. Contrasting to these reports of lower DAT in alcoholics, a recent PET study showed normal DAT levels in alcoholics.[59] The discrepancy probably relates to the time interval between the study and the last use of alcohol because the DAT are subject to rapid up and down regulation in response to drug challenge.[60]

SPECT studies with [^{123}I]β-CIT (a radioligand that measures serotonin transporter availability in the brain stem as well as DAT in the striatum) revealed a 30% decrease in availability of brainstem serotonin transporters in alcoholics, correlating with lifetime consumption of alcohol and with ratings of anxiety and depression during withdrawal.[61] In another PET study, [^{11}C]dihydrotetrabenazine, a radiotracer for the type 2 vesicular monoamine transporter (VMAT2), revealed reduced striatal VMAT2 indicating that nigrostriatal monoaminergic terminals are reduced, with or without loss of neurons from the substantia nigra and suggesting that the damaging effects of severe chronic alcoholism on the central nervous system are more extensive than previously considered.[62]

Imaging studies have also investigated gender differences in alcoholism. It is generally believed that women are more vulnerable to alcohol's toxic effects than men. However, while male alcoholics have consistently shown reductions in brain glucose metabolism relative to comparison subjects, a recent PET study with ^{18}FDG in 10 recently detoxified female alcoholics reported no differences between alcoholics and control females.[63] These results do not support a higher toxicity for the effects of alcohol in the female brain, as assessed with regional brain glucose metabolism.

However, the severity of alcohol use in these female alcoholics was less than that of the male alcoholics and thus additional studies in male subjects with alcoholism of moderate severity are required to confirm gender differences in sensitivity to the effects of alcohol on brain metabolism. Another study comparing male and female alcoholics suggests that alcohol has a differential effect on GABA-BZR in men and women.[64]

SPECT studies of blood flow have been recently used to examine the neurophysiological mechanisms of naltrexone therapy for alcoholism using a naltrexone challenge and SPECT-Tc-99m-HMPAO serial study design in chronic alcoholic patients during detoxification.[65] After naltrexone, a significant rCBF decrease was found in brain regions rich in opioid receptors (basal ganglia and left mesial temporal lobe) that may reflect a naltrexone-induced decrease in metabolism supporting the involvement of the opioid system in alcohol dependence.

NICOTINE AND TOBACCO SMOKE

It is estimated that half of the 45 million current smokers in the United States will die prematurely from a smoking related disorder.[66] The effects of tobacco smoke exposure on the human brain have recently been examined using imaging techniques.[67] Nicotine itself has been labeled with carbon-11 and its kinetics in the human brain show rapid uptake and egress characteristic of many drugs of abuse (reviewed in[68]). However, the PET image is dominated by non-specific binding limiting its use to the measurement of drug disposition and kinetics rather than to the examination of specific nicotine binding sites. Accordingly, there is considerable effort to develop radioligands with high specificity for imaging brain nicotinic receptors both for studies of addiction and as scientific tools in drug research and development.[68,69] Preclinical studies in the baboon model using one of these radiotracers, [^{18}F]norchlorofluoroepibatidine, show that ≈50% occupancy of the nicotinic acetylcholine receptors occurs at plasma nicotine levels similar to those attained during smoking.[70] However, the high toxicity of this radiotracer and others related to the epibatidine structure have precluded development for human studies.[71] Instead less toxic and more specific radioligands are under development.[68,72] Very recently, imaging of the $\alpha_4\beta_2$ nicotinic acetylcholine receptor in human was reported with [^{123}I]5-iodo-3-[2(SD)-2-azetidinylmethoxy]pyridine and the regional brain distribution was consistent with the known distribution of these binding sites.[73]

Though there is now no doubt that nicotine is the addictive component of cigarette smoke, tobacco smoke contains several thousand chemical compounds and some of these may also contribute to some of its behavior and toxic effects. One of the recently identified molecular targets for tobacco smoke is monoamine oxidase (MAO), an enzyme which breaks down neurotransmitter amines. It occurs in two forms, MAO A and MAO B that have different substrate and inhibitor specificities.[74] PET studies of MAO A and B have been carried out in smokers (for a review see Fowler et al[75]). PET studies of normal volunteers with the MAO A and B specific radiotracers [^{11}C]clorgyline and [^{11}C]L-deprenyl-D_2 revealed that cigarette smokers have reductions of 30% and 40% being observed for MAO A and B respectively.[76,77] Recent studies have shown that MAO B activity does not recover measurably with an overnight smoke-free interval and that no measureable MAO B inhibition occurs in non-smokers who smoke a single cigarette (reviewed by Fowler et al[75]). Taken together, these two studies indicate that the reduction in MAO B in smokers occurs gradually and requires chronic tobacco smoke exposure. Since MAO A and B break down dopamine, reduced MAO A and B in the smoker may spare brain dopamine and contribute to the behavioral and epidemiological effects of tobacco smoke. A recent study measuring platelet MAO B and its recovery during smoking cessation provides evidence that MAO inhibition from non-nicotine constituents in cigarette smoke is relevant to tobacco dependence and that the use of MAO inhibitors in smoking cessation merits continued investigation.[78] Along this line it is interesting to note that a MAO inhibitor compound has recently been isolated from tobacco leaves.[79]

In addition to studies of MAO, SPECT and PET have been used to examine the effects of smoking on the dopamine and the serotonin systems. A recent PET study of dopamine D1 receptor availability using [^{11}C]SCH23390 revealed a significant reduction in receptor availability in smokers relative to non-smokers particularly in the ventral striatum. This suggests that the post-synaptic mesolimbic dopamine system may be chronically

understimulated in smokers either as an antecedent or as a consequence of smoking.[80] Presynaptic dopamine activity was recently compared in non-smokers and in smokers using PET and [^{18}F]fluoroDOPA.[81] Significantly higher [^{18}F]fluoroDOPA uptake was observed in both putamen and caudate in smokers than in non-smokers indicating greater dopamine activity in smokers. This is consistent with previous reports of reduced brain MAO in smokers as more dopamine may be directed toward dopamine synthesis rather than to metabolism by intracellular MAO. A recent SPECT study with [^{123}I]β-CIT to assess DAT as well as serotonin transporter availability revealed that DAT levels do not differ between non-smokers and smokers but that serotonin transporters may be regulated by smoking in a sex-specific manner.[82]

Activation studies have also shown that non-smokers and smokers differ with respect to reward processing.[83] Pharmacological challenge studies with nicotine revealed different brain blood flow patterns between non-smokers and smokers when they perform a memory task.[84] It was also recently reported that a challenge dose of nicotine produces an increase in brain metabolism in the thalamus, a brain region with a high density of nicotinic acetylcholine receptors.[85] Blood flow increases were also observed in the thalamus in overnight abstinent smokers given a challenge dose of nicotine spray.[86]

OPIATES

Mu, delta, and kappa opioid receptors are the physiological targets of both endogenous and exogenous opioids.[87] PET and SPECT have been used to study opiate abuse in current heroin abusers, in individuals treated with opiate agonists such as methadone, and in those undergoing opiate withdrawal. Parameters measured include brain metabolism, neuroanatomical correlates of craving, opiate receptor occupancy with treatment drugs, and dopamine receptor levels at baseline and during acute withdrawal.

Similar to the effects of an acute dose of cocaine on brain metabolism in the cocaine abuser,[88] an acute dose of morphine in the opiate user results in an overall decrease in brain glucose metabolism.[89] The long term effects of opiate use on brain metabolism have also been examined with PET and ^{18}FDG.[90] This study revealed a significant differences in brain metabolism in the anterior cingulate gyrus between methadone-withdrawn subjects and a control group though it is possible that these neurochemical abnormalities that antedated the addictive behavior. A SPECT study with ^{99m}Tc-HMPAO assessing perfusion abnormalities in heroin dependent patients during withdrawal revealed perfusion abnormalities that were most pronounced in the temporal lobes and were not due to the conditions of withdrawal.[91]

A recent study has addressed the question of whether opiate addicts and control subjects respond differently to prototypical human rewards using PET and measures of rCBF using O-15 water during three types of feedback: nonsense feedback; nonmonetary reinforcement; or monetary reward.[92] In control subjects rCBF increases in regions associated with the dopaminergic system responded to both monetary reward and nonmonetary reinforcement whereas these regions were activated only in response to monetary reward in opiate addicted individuals. The authors attribute these differences to the direct effects of psychoactive drugs on the dopaminergic system and conclude that group differences can be attributed to an adaptive consequence of the addiction process.

The brain circuitry associated with craving was examined with PET and O-15 water in 12 abstinent opiate-dependent subjects.[93] A comparison of brain activation during craving and during a neutral episode revealed activation of rCBF in the left medial prefrontal and left anterior cingulate cortices and deactivation in the occipital cortex in response to the drug-related stimulus. There was also a positive association between craving and rCBF. The authors conclude that the patterns of brain activation reflect the different brain regions mediating the salience of opiate-related stimuli and the subjective experience of craving for opiates. In another study using PET and O-15 water in current intravenous heroin users[94], self-reports of "urge to use" correlated strongly with increased regional blood flow (rCBF) in the inferior frontal and orbitofrontal cortex, which are target regions of the mesolimbic dopaminergic system. The "urge to use was also associated with increased rCBF in the right precuneus, an area associated with episodic memory retrieval, and in the left insula, an area associated with the processing of the emotional components of stimuli. Self-reports of feeling "high" correlated with rCBF activation in the

hippocampus, an area relevant to the acquisition of stimulus-associated reinforcement.

Imaging has also been used to measure the degree of occupancy of opioid receptors by methadone, in methadone-maintained former heroin addicts (MTP) and a group of healthy normal control subjects using PET, and [^{18}F]cyclofoxy, a non-selective opioid antagonist radiotracer.[95] Results were compared to non-medicated normal volunteers. Specific binding was lower by 19 to 32% in these regions in MTPs and correlated with plasma levels of methadone suggesting that lower levels of binding may be related to receptor occupancy with methadone. This study also showed that even during methadone maintenance, a significant numbers of opioid receptors may be available to function in their normal physiological roles. In another PET study, mu opioid receptor occupancy by two different doses of buprenorphine (BUP, which is being evaluated as a treatment for heroin addiction) was examined using the mu subtype-specific PET radiotracer [^{11}C]carfentanyl.[96] BUP induced dose-dependent reductions in mu opiate receptor availability relative to placebo. This study design has the potential to examine the relationship between mu opiate receptor availability and therapeutic response in opiate abusers.

The role of the dopamine system in opiate withdrawal and dependence has also been investigated using PET.[97] Dopamine D2 receptor availability was measured with [^{11}C]raclopride in 11 opiate-dependent subjects at baseline and during naloxone-precipitated withdrawal. Baseline measures for dopamine receptor availability were significantly lower in opiate-dependent subjects than in controls similar to findings in other addictions. However, though naloxone precipitated an intense withdrawal in the abusers it did not produce the expected change in dopamine concentration.

MARIJUANA

Marijuana is the most widely used illegal drug of abuse in the United States and thus the nature of its effects on the brain are of major importance. Though the mechanisms by which Δ^9-tetrahydrocannabinol (THC) (main psychoactive substance of marijuana) exerts its psychoactive effects are still not fully understood, they may occur through its interaction with cannabinoid receptors which are highly localized in the cerebellum and the hippocampus.[98]

The functional effects of chronic marijuana smoking as well as those occurring with acute intoxication with smoked marijuana and injected THC have been measured with PET and with 0-15 labeled water and ^{18}FDG, respectively (reviewed in[4]). A recent PET study with 0-15 water compared rCBF in a group non-using control subjects and a group of frequent marijuana users after a 26 hour monitored abstention showed substantially lower brain blood flow than controls in a large region of posterior cerebellum, indicating altered brain function.[99]

The brain regions involved in the intoxicating effects of marijuana on cognition and brain function have also been assessed with PET and 0-15 water in recreational users before and after smoking a marijuana cigarette as they repeatedly performed an auditory attention task.[100,101] Following smoking, blood flow increased in a number of paralimbic brain regions (eg, orbital frontal lobes, insula, temporal poles) and in anterior cingulate and cerebellum. In contrast, rCBF decreased in temporal regions that are sensitive to auditory attention effects. The authors speculate that the intoxicating and mood related effects of marijuana may be mediated by brain regions showing increases in rCBF while decreases in rCBF in temporal lobes may be associated with impaired cognitive function during intoxication. In another blood flow study with injected THC challenge, decreased cerebellar function (which is linked to an internal timing system) occurred and may underlie alterations of time sense that is common following marijuana smoking.[102]

Since the measurement of the effects of THC and marijuana on blood flow may be confounded by the vasoactive properties of THC, PET measurements of brain glucose metabolism with ^{18}FDG (which is insensitive to fluctuations in blood flow) have also been used to assess acute effects of THC. PET studies have been performed in non abusing controls[103] as well as in marijuana abusers[104] in which subjects received a baseline PET scan with ^{18}FDG and a second scan after the intravenous administration of THC. Though the whole-brain metabolic response to the effects of THC was variable among individuals, there was a pattern of cerebellar activation by THC consistent with the high cerebellar concentration of cannabinoid receptors. Since the cerebellum is involved in motor coordination, activation by THC could ex-

plain the disruption in motor coordination during THC intoxication.

While the direct examination of cannabinoid receptors in the brain would be of great interest, developments in this area have been hampered by the high lipophilicity of THC. Recently, however, an iodine-123 labeled THC antagonist was developed and shown to bind to THC receptors in the baboon brain in vivo.[105] Thus, in the future it may be possible to examine the effects of THC on the human brain from the perspective of its binding to cannabinoid receptors.

INHALANTS

Inhalant abuse is a rapidly growing abuse problem especially in children. Neuroimaging provides the opportunity to examine some of the acute and chronic effects of inhaled solvents on the human brain. A recent study of rCBF with SPECT and N-isopropyl-p[^{123}I]iodoamphetamine in 16 chronic solvent abusers documented regional flow abnormalities particularly in the prefrontal cortex.[106] The degree of hypoperfusion was correlated with the severity of avolition-apathy suggesting that rCBF abnormalities, especially in the prefrontal cortex may underlie, which may be associated with lack of motivation and poor social prognosis. Another SPECT study with Tc-99m-HMPAO evaluated brain perfusion in long-term inhalant abusers of toluene, acetone, benzene, and derivatives and showed serious hypo-hyperperfusion foci and non-homogeneous uptake of the tracer.[107] In a preclinical PET study in the baboon, toluene, the major solvent of abuse was labeled with carbon-11 and its regional distribution and kinetics studied with PET in the anesthetized baboon brain.[108] High and rapid uptake of toluene into striatal and frontal regions of the brain was observed followed by rapid clearance of the brain. Interestingly, the kinetic pattern paralleled time course of the acute behavioral effects of toluene in humans.

VULNERABILITY

The questions of why some people who experiment with drugs become addicted while others do not is important in the context of understanding addictive behavior. One of the hypotheses is that there are individual genetic factors, that make some individuals more vulnerable to addiction. The "reward deficiency hypothesis" postulates that addictive behaviors, both pharmacological and non-pharmacological (gambling, for example) emerge as a result of understimulation of reward circuits with the drug taking or other behavior being used to stimulate these reward circuits. Indeed a variant on the dopamine D2 receptor (the Taq1 A_1 allele) has been reported to occur more frequently in individuals with abnormal appetitive behaviors.[109]

The observation of low dopamine D2 receptors in a number of abnormal appetitive behaviors (cocaine, heroin, alcohol, obesity[110]) coupled with the large dopamine D2 receptor variability in normal non-addicted individuals stimulated a study to examine whether healthy, non-drug abusing individuals with low dopamine receptor availability would respond differently to a challenge with a stimulant drug (methylphenidate) than individuals with high dopamine receptor availability.[111] Low dopamine D2 receptor level individuals found methylphenidate pleasant while, on average, high receptor level individuals found it unpleasant. This supports the notion that individuals with low dopamine receptors may have an understimulated reward system and as a result they perceive a pleasurable sensation when subjected to a drug-induced elevation in dopamine.

This study also suggests that high dopamine receptor levels may be protective against addictive behavior and that the elevation of dopamine D2 receptor levels may be therapeutically relevant in addiction treatment. This was probed in a preclinical study in which alcohol self-administering rats received an intrastriatal injection of an adenovirus carrying the dopamine D2 receptor to over-express dopamine D2 receptors. Dopamine D2 receptor overexpression occurred and was associated with a decrease in alcohol drinking in these animals. Drinking behavior resumed after several days and was associated with the expected decrease in gene expression with time.[112] Along this line, the use of various knockout animals hold promise as an important tool in characterizing the role of different cellular elements in addictive behavior[113] particularly when combined with microPET technology.[114]

IMAGING AND ADDICTION TREATMENT

Though addiction treatment has never been a priority in the pharmaceutical industry, many investigators have explored strategies for addiction treatment using animal models and limited clinical

trials.[115] Along this line, there is a major effort to develop drugs that antagonize the ability of cocaine to increase dopamine concentration thereby interfering with its reinforcing effects. It has recently been shown that increases in DA caused by drugs of abuse can be modulated trans-synaptically by enhancing levels of the inhibitory neurotransmitter GABA with the anti-convulsant drug vigabatrin (a suicide inhibitor of GABA transaminase).[116] GVG significantly attenuates cocaine and nicotine-induced dopamine release.[117,118] This biochemical effect has been shown both by microdialysis in freely moving rats and by PET in baboons using [^{11}C]raclopride, whose binding is reduced by elevations in synaptic DA. GVG also abolishes cocaine and nicotine induced behaviors such as self-administration and conditioned place preference in animals and clinical trials in cocaine abusers are currently being planned.

Since addiction is a complex disease, different therapies may be required for different phases of drug detoxification and rehabilitation. It is becoming more evident that the brain DA system is altered in addiction and that reduced brain metabolism in the orbital frontal cortex is associated with low brain dopamine activity.[24] However, if a decrease in brain dopamine function predisposes an individual to administer drugs of abuse as suggested by the reward deficiency syndrome hypothesis of addiction,[109] then cocaine "antagonist" drugs may not be sufficient to prevent relapse in these subjects. In this case, drugs that could help restore dopamine brain function could be therapeutically beneficial.

SUMMARY

There is overwhelming evidence that addiction is a disease of the brain, and neuroimaging studies of the pharmacokinetics and pharmaocdynamics of abused substances continue to document functional and neurochemical changes in the brain of the addicted subject and to link these to behavioral effects. As new knowledge emerges, it will be possible to develop more rational approaches to treatment. Imaging can be expected to provide the means to objectively link behavioral and neurochemical changes and to objectively evaluate treatment. In addition, with the identification of new genes related to addictive behavior, imaging promises to provide a tool for directly translating this knowledge to an evaluation in humans.

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