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Targeting the treatment of drug abuse with molecular imaging

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Abstract

Although imaging studies in and of themselves have significant contributions to the study of human behavior, imaging in drug abuse has a much broader agenda. Drugs of abuse bind to molecules in specific parts of the brain in order to produce their effects. Positron emission tomography (PET) provides a unique opportunity to track this process, capturing the kinetics with which an abused compound is transported to its site of action. The specific examples discussed here were chosen to illustrate how PET can be used to map the regional distribution and kinetics of compounds that may or may not have abuse liability. We also discussed some morphological and functional changes associated with drug abuse and different stages of recovery following abstinence. PET measurements of functional changes in the brain have also led to the development of several treatment strategies, one of which is discussed in detail here. Information such as this becomes more than a matter of academic interest. Such knowledge can provide the bases for anticipating which compounds may be abused and which may not. It can also be used to identify biological markers or changes in brain function that are associated with progression from drug use to drug abuse and also to stage the recovery process. This new knowledge can guide legislative initiatives on the optimal duration of mandatory treatment stays, promoting long-lasting abstinence and greatly reducing the societal burden of drug abuse. Imaging can also give some insights into potential pharmacotherapeutic targets to manage the reinforcing effects of addictive compounds, as well as into protective strategies to minimize their toxic consequences.
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1. The scope and agenda of positron emission tomography (PET) imaging in drug abuse research

Molecular imaging in drug abuse research can generally be conceptualized as a scientific discipline within the imaging field that strives to understand the mechanisms by which drugs abused by humans affect behavior, leading to loss of control, which in turn defines dependence and, eventually, addiction. In this respect, it is similar to imaging studies of other mental illnesses, the goals of which are to use molecular imaging to delineate the mechanisms by which drugs can ameliorate psychiatric conditions and also to identify those patients who will or will not respond to treatment. Over the last few decades, the scope of imaging in drug abuse research has expanded considerably. This has been driven, in part, by the unique ability of PET to map the regional distribution and kinetic profiles of abused drugs in the service of elucidating what makes them addictive, as well as by the use of PET to image complex molecular interactions that subserve human addiction and recovery. In this way, the use of PET in drug abuse research differs from the use of PET in other mental illnesses, which instead seeks to develop compounds or agents with specific behavioral actions for therapeutic purposes. Whereas functional brain imaging in mental illness seeks to identify functional disturbances underlying psychiatric disease and in vivo mechanisms by which medications ameliorate these conditions, imaging in the drug abuse field seeks to elucidate in vivo mechanisms by which specific agents commandeer natural motivational and drive circuits in an otherwise healthy brain.

As the above discussion implies, imaging in the drug abuse field actually has dual overlapping agendas. One derives from the growing recognition of drug abuse as a biological condition, removing the social stigma that affects patients, families and therapists. A goal within this agenda needs to be the widespread dissemination of information from human imaging studies that describe the time course of changes in the brain during acquisition of drugs and recovery

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from drug abuse or addiction. This information can be used by policymakers, lawmakers and insurance companies to guide the duration of treatment stays, promoting long-lasting abstinence. For example, decreases in dopamine transporter (DAT) density in the brain from chronic methamphetamine abuse are not ameliorated for at least 9 months after abstinence, yet most insurance policies will only cover a single month of rehabilitation, releasing individuals at what may be their most vulnerable biological point in the recovery process. With imaging, specific markers of the recovery process could instead be used to guide the release of patients at their strongest point in abstinence. Using this information, we should be able to identify different stages of specific addictions based on well-defined clinical, biological and neurological criteria. For each stage of the addictive process, specific therapeutic regimens that combine psychosocial intervention with several medications, used separately or in combination to target stage-specific neurochemical pathways, could be available. The benefits of such comprehensive therapeutic regimens, whose foundations lie in neuroimaging studies of human drug abusers, may include a sharp reduction in relapse and recidivism, deaths due to traffic accidents, AIDS, drug overdoses, cardiovascular diseases, hepatic diseases and cancer, as well as marked decreases in domestic violence and urban crime. The second agenda involves the more traditional role of imaging as the scientific discipline defined above, whose goal is to understand biological mechanisms by which drugs of abuse impact behavior. A goal within this agenda is to identify, monitor and quantitate physiological consequences of drug abuse, finding end points to stage the disease process, its recovery and the efficacy of potential pharmacotherapeutic treatments. This will facilitate the identification of new biological markers of addictive processes, as well as the development of candidate targets for pharmacotherapies.

Despite recent advances in neurobiology and the obvious utility of in vitro approaches to elucidating biological substrates of addictive behaviors, it is difficult to conceive of any substitute for assessing the ultimate impact of an abused compound on behavior or the behavioral mechanisms of abused compounds, other than in a whole behaving organism. Links between molecular neurobiology or between neuropathological alterations and the behavioral manifestation of dependence and addiction are still obscure. Although the relationship between certain neurotransmitters and behavior has become increasingly evident, such as the role of dopamine in reinforcing properties of abused drugs, other aspects of those relationships remain puzzling (e.g., that DAT knockout mice will still self-administer cocaine) [1]. Even more puzzling is the large body of evidence showing that humans will abuse virtually every drug that an animal will self-administer, yet drugs that block animal self-administration appear to be ineffective treatments in humans. In fact, there is no effective pharmacotherapeutic treatment for drug abuse in humans, despite many compounds shown to successfully reduce self-administration in animals. Thus, there are no substitute or alternative procedures for evaluating the active processes or functional impact of drug abuse in human studies of drug-abusing populations. Add to this the fact that brain imaging methods used to identify markers of addiction and recovery in humans have been largely inaccessible to animals, broadening the disconnection from animal models of drug abuse to drug-abusing humans. Molecular imaging, combined with simultaneous behavioral assays, provides an approach (in humans and animals) with which we can predict the complex behavioral effects of drugs by evaluating brain function at a molecular level. Furthermore, in animals and humans, behavioral measures can now be combined with simultaneous measures of brain physiology with a common outcome measure. Molecular imaging, thus, has the potential to unify decades of animal research with clinical populations under study.

Herein we discuss two important aspects of imaging that have made significant contributions to the study of drug abuse. The first aspect concerns the unique ability of PET over other imaging techniques to map the distribution and kinetics of abused drugs, in the service of elucidating physicochemical properties that may contribute to their observed reinforcing properties and abuse liability. As an example, we describe our own published work using PET and other imaging approaches combined with behavioral measures to identify which volatile solvents are likely to be abused and which have less abuse potential. In these studies, we have also carefully documented physiological consequences of inhalant abuse and the capacity of neural systems to rebound upon cessation of inhalant exposure. This leads to our second goal, which is to describe some biological markers of addiction that have been documented using PET in human drug abusers. Here we also emphasize the time course of morphological changes in the brain following abstinence from drug abuse. We propose that imaging dynamic measures of brain function, as opposed to static measures of brain morphology, may be a more sensitive assay of those molecular events that underlie the transition from drug use to drug abuse, dependence and, eventually, recovery following abstinence.

2. State of development

Although the capability for PET to precisely identify or stage drug abuse and addiction exists, the field is still largely at the characterization or descriptive stage of development. Any PET study involves a multiplicity of processes, which together result in a PET image and the pharmacokinetics that define that image. PET studies allow us to noninvasively observe physiological changes associated with addiction in terms of both anatomy and function. The ability to measure both of these components gives PET tremendous power to observe the entire addictive process. However, it is important to remember that PET is not used to define a biochemical

pathway in a single cell and that it does not compete with the elegant basic work or the structure and function of single cells or small groups of cells. By the same token (and this is one of the greatest strengths of PET), the ability to assay the dynamic activity of a large aggregate of cells in vivo in the human brain, involving systems with numerous complex interactions in quantitative terms, is exclusive to PET.

In general, PET studies of drug abuse and addiction use several different strategies (Table 1). First, distribution studies can be performed when a drug itself is radiolabeled and used to map regions where it accumulates and its kinetic profile in the brain and other organs. This approach uses PET to track the distribution of a small amount of drug, which may differ when the drug is abused or taken in much larger amounts. Second, at tracer doses (where only a small fraction of target proteins is occupied), images may reflect the local concentration of radiotracer-binding sites. This most commonly employs radioligands that bind with high specificity to one neuroreceptor but can also involve labeled precursors that concentrate in specific neurons. Neuroreceptor ligands have often been used in an attempt to differentiate normal brains from diseased brains in terms of baseline receptor parameters (B_{max} and K_d). Third, in pharmacological displacement studies, competition between a pharmacologically active dose of an abused drug and the binding of a specific tracer at the same site can be measured. Fourth, if a radiotracer and a neurotransmitter have a similar affinity for the same receptor site, displacement of the radiotracer gives an indirect index of endogenous neurotransmitter function. This approach can be used to examine dynamic rather than static parameters of complex neurochemical systems within the brain. One can ask, for example, "Does the normal brain differ from that of an addicted individual in its response to a single dose of an addictive or a therapeutic drug?" We can also use PET to look at coupled receptor systems or, put another way, at more than one neurotransmitter at a time. This displacement strategy measures the interaction between functionally linked neurotransmitters at the same receptor site by pharmacologically modulating one neurotransmitter and by measuring the displacement of a second related neurotransmitter. In this case, it is assumed that the number of receptors (expressed as B_{max}) is a fixed parameter that can be used to measure the acute response of one neurotransmitter system to a challenge targeting another. This strategy is predicated on the notion that neurochemical systems do not function in isolation and that some of the pathology contributing to drug addiction may involve the inability of one neurotransmitter to adequately control another. For example, γ-aminobutyric acid (GABA) is a ubiquitous inhibitory neurotransmitter that normally modulates the release of dopamine in the striatum. Over time, chronic drug abuse may impair the ability of GABA to control dopamine release. However, this simplified example does not do justice to the complexity of neurochemical systems in the brain. Our challenge is to elucidate changes in those multitransmitter pathways that lead from use to abuse and dependence, or perhaps to identify anatomical misconnections between neurotransmitters that manifest in different brain responses to a drug challenge. Finally, measures of blood flow or indirect assays of cerebral rates of glucose utilization use $^{15}O_2$-labeled water or fluorodeoxyglucose (FDG) labeled with fluorine-18 as radiotracers. As measures of brain function, these radiotracers can be used to measure differences in metabolism or blood flow associated with prolonged drug or alcohol abuse. In this study, they can also be used to measure the return of metabolism or flow following abstinence. These functional measures can elucidate patterns of brain activation associated with such behavioral states as drug craving.

Table 1
Experimental strategies for PET studies of abused compounds, their mechanisms of action and their neurotoxic consequences

1. Distribution	A compound can be labeled and administered, allowing a direct measure of its distribution in the brain and other organs. Many drugs of abuse have been labeled directly.
2. Density	At a 'tracer' dose (that which occupies only a small fraction of available binding sites; 1/1000 of a pharmacologically active dose in humans), A PET image may reflect the local concentration of drug_binding sites.
3. Pharmacological displacement	Competition between an abused drug and a different radiotracer that goes to the same site can be measured, making it possible to estimate the number of receptors that are occupied by the abused drug and the relationship of this action to feelings of euphoria.
4. Endogenous displacement	Competition between a radiotracer and a naturally occurring neurotransmitter at the same receptor site can give an index of changes in an endogenous neurotransmitter.
5. Interactions	Competition approaches can also assess the utility of potential treatments for blocking reward-related increases in mesolimbic dopamine.
6. Metabolic function or blood flow	PET can be used to measure either blood flow or cerebral rates of glucose utilization, using $^{15}O_2$-labeled water or 2-deoxy-2-[^{18}F]fluoro-D-glucose labeled with either ^{18}F or ^{11}C as a radiotracer. PET can measure the rate at which glucose is metabolized (local metabolic rate of glucose utilization), providing an index of changes in energy demand in specific areas of the brain during a mental activity such as drug craving.

3. Drug distribution and pharmacokinetics relate to abuse

3.1. The study of abused solvents

As an example of the application of PET to elucidate how drug distribution and pharmacokinetics relate to the probability that a given compound will be abused, we present studies of solvent or inhalant abuse. Virtually an epidemic of inhalant abuse in adolescents has taken place in recent years in nearly all industrialized and developing countries. Only

certain products, such as those containing toluene and benzene, are abused at epidemic proportions. It is not known what neurochemical properties underlie this preference, nor have the short-term or long-term effects of inhalant abuse on brain function been well established.

Although systematic animal studies of the relative abuse potential of different organic solvents have not yet been conducted, animal models describing the stimulus properties of these chemicals have been described. Nonhuman primates, for example, will self-administer inhaled vapors of toluene [2], and mice will intravenously self-administer toluene [3]. Studies in our own laboratory have used the conditioned place preference (CPP) paradigm to show that toluene is dose-dependently reinforcing [4,5]. In parallel, studies mapping the regional distribution and pharmacokinetics of radiolabeled toluene ([^{11}C]toluene) provide strong evidence supporting the reinforcing properties of this particular abused solvent. If similar results are found with other solvents, it may be possible to develop a systematic framework for evaluating the abuse potential of industrial and household compounds. A schematic of this framework is depicted in Fig. 1. In this experimental framework, we combined the CPP of inhaled solvents with data gathered from different neuroimaging tools to first identify the relationship between the regional distribution of a radiolabeled solvent, its pharmacokinetic and pharmacodynamic properties, the reinforcing value of a given solvent and, finally, the morphological and functional consequences of its abuse.

3.2. Pharmacokinetics, pharmacodynamics and abuse potential

PET has been particularly useful for establishing a link between the route of drug administration, pharmacokinetics and abuse liability. For example, studies using [^{11}C]cocaine and [^{11}C]methylphenidate have confirmed the dependence of drug reinforcement on the rate of brain uptake and clearance. These studies showed that the fast kinetics of [^{11}C]cocaine versus the slower kinetics of [^{11}C]methylphenidate directly correlated with subjective ratings of euphoria [6–9]. That is, studies using positron-labeled compounds demonstrated that while cocaine and methylphenidate bind to the same protein in the brain, delivery and elimination kinetics appear to dictate their reinforcing properties and subsequent abuse liability (also see Quinn et al. [10] for review).

It has also been well established that rapidly cleared drugs are associated with repeated self-administration, the best examples being intravenous cocaine [6,7], benzodiazepines [11] and barbiturates [12]. Using anxiolytics, these latter studies demonstrated a direct correlation between the pharmacokinetic rate of elimination and the rate of self-administration in primates [11]. This is especially germane to the study of solvent abuse, since inhalants share many

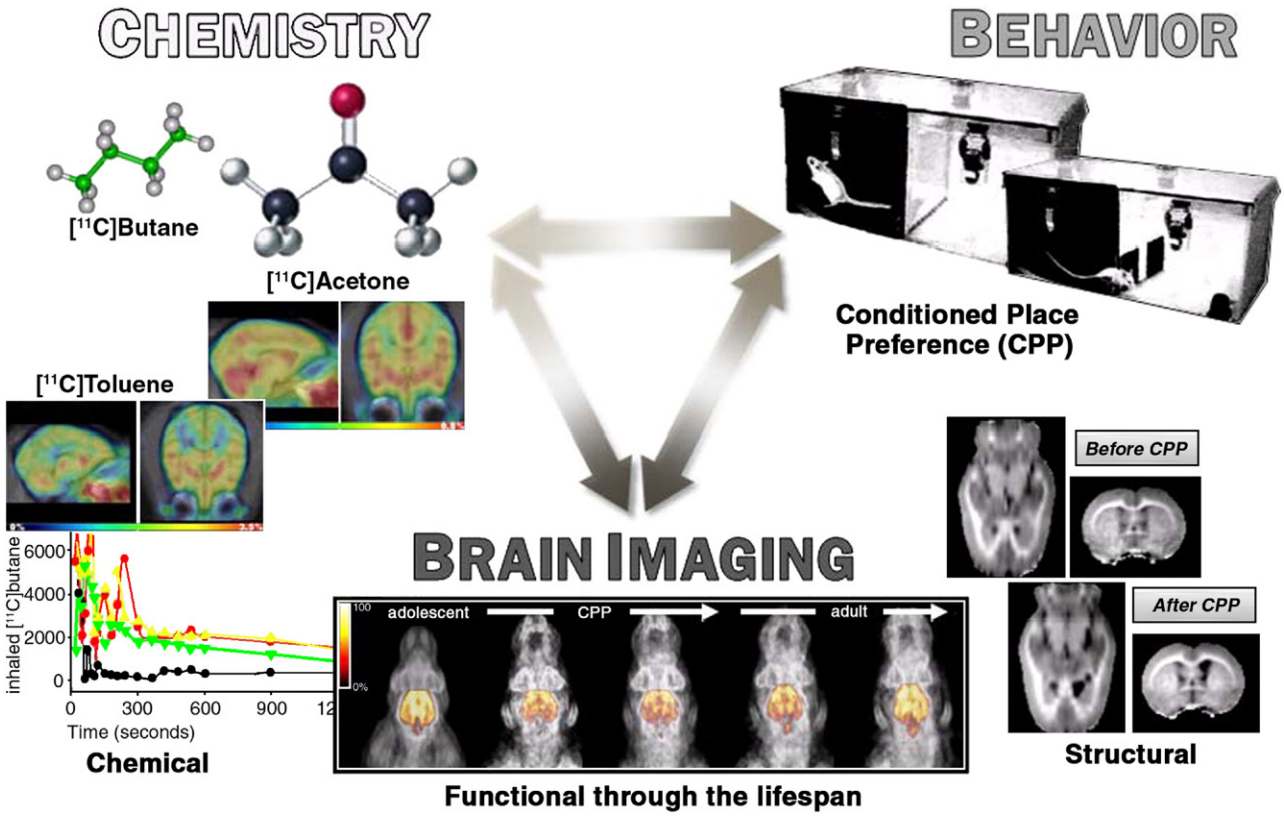

Fig. 1. Framework for behavioral imaging studies of potentially abused solvents. These studies are designed to identify the reinforcing properties of several inhaled solvents relative to their kinetics, their dynamics and the impact of these combined factors on brain structure and metabolic function from adolescence to adulthood.

biochemical and behavioral properties with benzodiazepines and barbiturates [13–16]. Thus, the rate of elimination, along with rapid absorption and entry into the central nervous system (CNS), high bioavailability, short half-life, small volume of distribution and high free drug clearance, is an important factor in predicting abuse potential, since these factors increase positive reinforcement [10,17,18]. Taken together, it follows that inhalants, which are rapidly cleared from the CNS, will have high abuse liability and that those that diffuse slowly into the CNS and have longer half-lives will have a lower reinforcing value. This pharmacokinetic profile, along with the distribution of these compounds in the brain, may underlie both preference for inhalants and detrimental consequences of their abuse.

Our proposition is that for commonly used inhaled solvents, reinforcing properties and narcotic CNS effects are closely related to the chemical structure of the solvent and its pharmacokinetics. We performed a number of nonhuman primate PET studies to establish the uptake and distribution of several potentially abused inhalants [19–22]. These studies provide evidence for common features of abused inhalants with similar physiochemical properties, but they also demonstrate that some compounds have a unique regional 'signature' of distribution and accumulation. For example, it is clear from these and other studies that the uptake and distribution of inhalants as a class can be largely attributed to factors including tissue lipid content and blood perfusion rates [19,20,23]. These same factors appear to affect inhalant distribution within specific regions of the brain for a more specific class of abused compounds. In fact, data in Fig. 2 support this 'signature' hypothesis by demonstrating that the distribution of different compounds in the primate brain is unique to the solvent. Similarly, the kinetics with which different solvents enter and exit these regions is also different. It has previously been shown that, unlike toluene, which distributes preferentially to lipid-rich regions of the brain, acetone prefers regions on the basis of water content [25], with a slow rate of disappearance from the blood following zero-order kinetics. In agreement, it is evident in Fig. 2 that the initial distribution of [^{11}C]acetone in the primate brain resembles that of [^{15}O]water, where, at the same time, [^{11}C]toluene and [^{11}C]butane distribute immediately from the blood into lipid-rich regions of the brain. Thus, the degree to which a compound accumulates in a given region of the brain most likely influences the function of this region. As we present below, the speed at which a compound enters and leaves a region is also critical to its abuse liability.

In terms of kinetics, since acetone is more water soluble than toluene, following inhalation, it would be expected to rapidly enter the blood and other body fluids but slowly diffuse into the CNS and other lipid-containing tissues. In fact, we have shown that [^{11}C]acetone diffuses slowly into the brain and that its clearance is markedly slower than that of [^{11}C]toluene [19]. Taken together with evidence that fast brain uptake and clearance are associated with high abuse liability [7,26], it follows that the reinforcing properties of acetone are much less than those of toluene. Below we describe behavioral evidence to support these pharmacokinetic predictions.

3.3. Bridging experimental animal and human behaviors

Although children appear to be in the high-risk group, solvent abuse can occur in drug-seeking adults as well as in occupational settings. In fact, many of the case studies reporting persistent CNS effects involved adults whose initial experience with euphoric effects of abused solvents occurred in an occupational setting, unrecognized by these exposed workers as being associated with the chemical effects of solvent. As an example, Knox and Nelson [27] described a man who felt euphoric while working with paint thinner at an aircraft manufacturing company. His insistent requests to continue working in the capacity that employed the paint thinner went unnoticed. Eventually, his habit escalated to deep inhalations of concentrated vapors from a small container throughout the day. This behavior persisted for over 14 years. This case report and many others [28,29] describe accidental exposures that possess striking similarities to animal models of inhalant abuse using the CPP paradigm. It follows that a critical component in bridging experimental animal and human drug abuse research

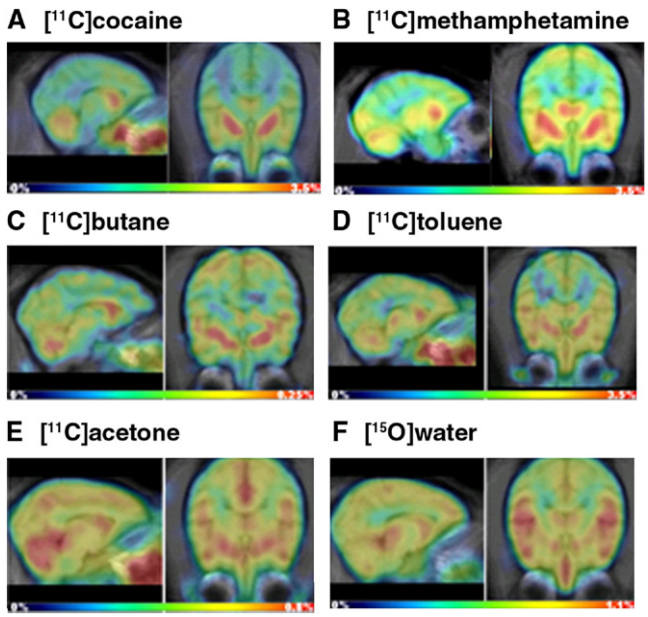

Fig. 2. Radioactivity distribution of abused or potentially abused compounds in the primate brain. The distribution of two compounds with established abuse liability, [^{11}C]cocaine (A) and [^{11}C]methamphetamine (B), can be compared to compounds with questionable abuse liability, such as [^{11}C]butane (C), [^{11}C]toluene (D) and [^{11}C]acetone (E). [^{11}C]Acetone is thought to distribute to brain regions based on water content due to its high water solubility, which is evident in a similar distribution of [^{11}C]acetone and [^{15}O]water (F). Radioactivity distribution images are coregistered atlas spaces using the template provided by Black et al. [24], which also includes the [^{15}O]water PET image shown in (F).

strongly emphasizes the use of applicable behavioral paradigms. With specific regard to solvent abuse, CPP exemplifies one such class of behavioral measures.

In the CPP paradigm, a drug-free animal is placed in a contextually distinct environment where solvent vapors are introduced. On alternating days, the animal is placed in a different environment where air is introduced, such that the animal is conditioned to associate one environment with a particular solvent, while the other environment becomes neutral. After a specified number of these 'pairings,' animals are given a choice of the two environments (in a drug-free state), and the reinforcing value of the solvent is assessed by the duration of time spent in a solvent-paired chamber. Thus, just as adults at risk for solvent abuse include those whose work brings them into contact with these substances, such as shoemakers, painters and people working with gas and jet fuel [29], animals exposed to certain solvents in a particular environment develop a preference for that environment over the neutral one [4,30,31].

In fact, our group and others have used the CPP to demonstrate that toluene is dose-dependently reinforcing in both adolescent and adult animals [4,5]. We also demonstrated that the expression of toluene-induced place preference can be reversed by prior treatment with a drug that increases brain GABA [32]. Given an established method to evaluate the salient properties of inhaled solvents, we hypothesized that acetone, with its high water solubility, slow brain diffusion and longer half-life, would be less reinforcing than toluene. In fact, over a wide range of concentrations and exposure durations, acetone failed to produce any reinforcing properties. Thus, in this case, our PET studies examining distribution and pharmacokinetics accurately predicted the reinforcing properties of toluene over acetone.

In sum, speed of induction and depth of intoxication depend on the concentration of the solvent inhaled by animals and humans, and these are directly related to brain and blood concentrations, pharmacokinetics and the dynamics of the interaction between a given solvent and the CNS. It has been suggested that similar CNS effects would be experienced by humans and small animals with equivalent tissue levels of a volatile solvent [25,33], although the exposure time for attaining such a level would be longer in humans due to their lower volume of breathing per kilogram of body weight [34]. In the case of solvents, these abusers typically inhale rapidly and very deeply, so their respiratory uptake may be roughly equivalent to that of rodents. In fact, Haggard [33] demonstrated that the accumulation of acetone in the blood of a human performing moderate exercise approached that of a resting rat breathing the same concentration of acetone vapor. It has also been shown that humans eliminate acetone from the blood at roughly half the rate of rats [33] and that exhalation was the predominant mechanism for eliminating large doses of acetone. Finally, experimental animal and human studies of drug abuse have common goals: to understand the mechanisms by which solvents affect behavior and to implement procedures to screen for compounds with abuse potential, as well as for markers indicative of recovery, as discussed below.

4. Molecular targets of drug abuse and recovery

PET is uniquely suited to measure changes in synaptic neurotransmitter responsiveness or physiology in the living brain. This approach can be used to assess the functional integrity of neurotransmitter systems and the multiple mechanisms of drug action. In this study, the development of radiotracers for studying various systems remains one of the major thrusts of PET research. At this point, a broad spectrum of radiotracers has been developed and applied to the study of the brain, with special focus on drug mechanisms and physiological changes associated with drug addiction.

Addiction is often defined as a loss of control of drug use or the compulsive seeking and taking of drugs despite adverse consequences. Drug abuse can be defined as excessive and potentially harmful drug use, whether or not the subject is addicted to this drug. Both addicted and nonaddicted abusers have changes in brain chemistry that can be captured with imaging. All drugs of abuse initially interact with specific receptor or reuptake proteins, which, depending on the pharmacokinetic and pharmacodynamic properties of the drug, produce a chain of events that activates a central reward system in the brain. Given that drugs with different mechanisms can produce similar rewarding behaviors, it follows that the mechanism of the drug per se might not be as responsible for drug dependence, as subsequent physiological adaptations most likely extend beyond the initial site of action. Neural circuits within the mesolimbic/mesocortical system have been identified to mediate the acute reinforcing effects of most abused drugs [35]. The addictive liability of many abused drugs appears to be a function of the magnitude to which they increase dopamine activity in these regions [36,37].

In humans, both the effects of drug intake on emotional variables and the motivation for drug seeking usually initially depend on psychological variables (i.e., stress) and individual differences in sensitivity and response. For example, PET studies with the high-affinity dopamine D_2 receptor ligand [18F]*N*-methylspiroperidol and indices of glucose metabolic activity with ^{18}FDG suggest that the disruption of mesocortical dopamine systems from chronic cocaine use leads to abnormal glucose metabolic activity in terminal — primarily cortical — areas [38]. Dysregulation of these frontal regions in cocaine-addicted patients might favor the emergence of behaviors associated with addiction, such as the loss of control leading to compulsive drug-taking behavior. Thus, the central reward system of the brain appears to integrate individual variables and to adjust drug seeking and drug taking accordingly.

Although the initial effects of rewarding drugs on the brain are related to alterations in the dopaminergic system, it

is likely that the development of drug dependence is also a function of the ability of dopamine to modulate, or be modulated by, other neurotransmitter systems. Serotonin, GABA, glutamate and dopamine neurotransmitter systems continually interact to maintain a level of functional homeostasis, such that changes in one system may be compensated for by endogenous alterations in a related system. In turn, each of these neurotransmitter systems plays a specific role in mediating behaviors associated with drug dependence, such as craving, stress or withdrawal. Thus, although addiction has been classically attributed to isolated changes in the dopamine system, each of these systems is most likely modified during the development of dependence and appears to remain sensitive to future perturbations.

For example, by blocking dopamine reuptake sites, cocaine produces a dose-dependent increase in synaptic dopamine. The expression of dopamine-mediated behaviors requires the activation of GABA pathways [39], which are therefore a particularly susceptible target for cocaine's effects. Furthermore, chronic cocaine use might alter the responsivity of the GABA system to perturbation of the dopaminergic system. Consistent with this hypothesis, studies in our laboratory have demonstrated that cocaine-dependent subjects have an enhanced metabolic response to a drug targeting the GABA system [40]. In addition, there appear to be significant reductions in striatal dopamine D_2 receptors in cocaine-dependent subjects that persist long after detoxification [41,42]. Taken together, these findings suggest the involvement of GABA in dopamine abnormalities characteristic of chronic cocaine abuse.

Since the dopamine system appears fundamental to addiction, many PET studies have focused on measuring physiological and functional alterations within this system. It is important to clarify the different ways in which PET is used to study these adaptations. First, PET studies exploring physiological alterations in the brain typically employ radiotracers with a high affinity for a given dopamine receptor (either presynaptic DATs or postsynaptic D_2 receptors). This ensures that the binding of the radiotracer will not be influenced by changes in synaptic dopamine, since they are presumably both competing for the same receptor site [43]. Second, PET studies exploring dynamic fluctuations in radiotracer concentrations use radiotracers with moderate receptor affinity, comparable to or lower than that of dopamine itself. The theory behind this approach is that radiotracers with a similar affinity for a given receptor site as dopamine can be displaced by increases in dopamine and are thus sensitive to changes in synaptic dopamine concentrations [44]. For example, increases in synaptic dopamine have repeatedly demonstrated the ability to reduce the binding of the moderate-affinity D_2 radiotracer [^{11}C]raclopride [44–48]. The reverse holds true for decreases in synaptic dopamine, such that drugs that inhibit dopaminergic systems increase the binding of [^{11}C]raclopride [49–52]. This allows quantification of changes in the releasable pool of dopamine resulting from chronic drug abuse, and chronic exposure to a psychostimulant might diminish dopaminergic response to a drug challenge without affecting receptor number. It is important to distinguish between the two and to ensure that radiotracer measurements intended for static receptor density are not confounded by changes in dopamine.

4.1. PET studies of cocaine addiction

Cocaine possesses a reward value such that laboratory animals, given free access, will self-administer until death [53]. This phenomenon may distinguish cocaine from other drugs of abuse, since most are not self-administered at the expense of self-preservation. In humans, cocaine is a widely abused drug [54] is also associated with major medical problems such as myocardial infarction, seizures and psychosis [55]. Acute cocaine administration increases subcortical dopamine levels by blocking DAT, preventing reuptake and subsequent catabolism [56]. Studies in primates revealed that the binding of [^{11}C]cocaine in the striatum is reduced by prior treatment with nomifensine, a drug that binds to DAT sites, supporting in vitro evidence that cocaine binding occurs in a site associated with DAT [57]. When animals were pretreated with other drugs that inhibit norepinephrine and serotonin transporters, [^{11}C]cocaine binding was not altered [58]. These studies provide strong evidence that while mechanisms for cocaine's reinforcing properties are complex, they primarily involve the brain dopamine system and, in particular, DAT [59]. Given that PET measures the regional distribution and kinetics of radioisotopes in tissues of living subjects [60], it has been used to address these measurements with respect to cocaine's behavioral and toxic effects.

These distribution studies have yielded several observations of significant biological characteristics that relate to cocaine's abuse liability. First, pharmacokinetic PET investigations of [^{11}C]cocaine in the brain indicate maximal uptake in the striatum. Fig. 3 presents radioactivity distribution in the human brain, the primate brain and the rodent brain, as measured with PET. Kinetic information underlying images such as these has been used to demonstrate that the dose of cocaine typically used by cocaine-addicted patients (~25–50 mg/kg iv) [62] occupies roughly 60–80% of DAT high-affinity sites [63], although given considerations of pharmacokinetics, these occupancies might be underestimated. Second, these studies demonstrate a very rapid uptake kinetics of [^{11}C]cocaine, with a peak concentration at 4–8 min after injection. Previous studies suggest that the rate of change at which total DAT occupancy is achieved will affect the intensity of cocaine's effects [64,65]. When compared with the DAT inhibitor methylphenidate (Ritalin), which is much less addictive and clears from the brain at a much slower rate than cocaine, it appears that, once again, pharmacokinetics plays a critical role in the addictive liability of abused substances [65]. Thus, while the relationship of DAT blockade to euphoria can be estimated, it is also logical to assume that higher doses will achieve blockade of more

DAT sites faster and that a higher proportion of blocked sites will be maintained for a longer period of time [65]. In this study, just as we demonstrated with inhalants, analyses of the pharmacokinetic behavior of cocaine in the human brain reveal that it is not only distribution that makes cocaine uniquely addictive but also kinetics.

DAT, located on the presynaptic terminal of dopamine neurons, is also a marker for the integrity of these neurons. These tracers, therefore, have particular value in monitoring the progress of neurodegenerative and neuroregenerative processes associated with chronic drug abuse. For example, a logical prediction would be that, through prolonged initial targeting of the DAT protein, chronic cocaine abuse might induce compensatory alterations in the density of these sites. However, when [^{11}C]cocaine was used to evaluate DAT in 12 detoxified cocaine abusers compared to 20 age-matched controls who had never used cocaine [66], there were no significant differences between the two cohorts in the specific binding of [^{11}C]cocaine. The only difference between cocaine abusers and controls in these studies appeared to be a dramatically reduced global uptake of radiotracer, which was decreased in all regions of the brain. Thus, once again, while PET studies alone have elegantly identified the initial site of cocaine binding in the brains of humans and animals, there is evidence to suggest that these targets may be necessary but not sufficient for the reinforcing value or the chronic impact of cocaine abuse.

4.2. PET studies of methamphetamine abuse

Methamphetamine is a popular and highly addictive drug of abuse that has raised concerns because it is neurotoxic to dopamine terminals in animal studies [67]. While mechanisms of methamphetamine are unclear, it appears to increase the synthesis of dopamine [68]. PET studies using radiotracers with a high affinity for DAT have demonstrated significant reductions in DAT density in methamphetamine abusers [67,69,70]. These studies provide strong evidence for the loss of DAT or dopamine terminals, and they raise the possibility that, as this population ages, they may be at increased risk for the development of parkinsonism or neuropsychiatric conditions associated with a diminished activity of dopamine neurons [69]. In fact, reduced DAT density in the caudate/putamen and nucleus accumbens has been associated with the duration of methamphetamine use and appears to be closely related to the severity of persistent psychiatric symptoms [71].

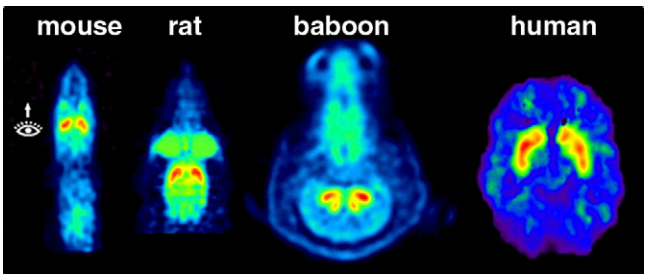

Fig. 3. Translational neuroimaging: [^{11}C]cocaine binding across species. PET captures the radioactivity distribution of [^{11}C]cocaine from mouse and rat brains, the *Papio anubis* baboon brain and the human brain. Rodent PET data were obtained with a microPET R4 scanner; primate and human images were obtained with an ECAT HR^{+} tomograph. Rodent and baboon brains are reconstructed using maximum a posteriori (MAP) algorithm for increased resolution [61]. MAP-reconstructed [^{11}C]cocaine images of the primate are courtesy of Drs. Evren Asma and Richard Leahy. Radioactivity distribution images are colored using an extended rainbow color scale, where red and white represent image pixels with the highest radioactivity values.

Because significant reductions in DAT occur both with age (6–7% in each decade from 20 to 80 years of age [72]) and with methamphetamine abuse (equivalent to that seen in those aged >40 years), a concern arises as to whether DAT losses in methamphetamine abusers will place them at risk for parkinsonism as they age. The extent to which this is likely to occur depends, in part, on the reversibility of changes induced by methamphetamine abuse. Recent studies in rodents [73,74] and nonhuman primates [75] have revealed significant recovery in DAT proteins with protracted abstinence. This suggests that either methamphetamine-induced damage to dopaminergic terminals recovers with time or DAT losses reflect adaptive changes rather than neurotoxicity.

Recent studies have observed a significant recovery of DAT with protracted abstinence in methamphetamine abusers who were able to stay drug free after the initial evaluation [76,77]. Moreover, larger increases in DAT were observed with longer periods between evaluations, providing strong evidence that DAT recovery is, in part, a function of the length of the abstinence period [77]. Interestingly and perhaps most relevant to using DAT as a marker for recovery from methamphetamine abuse, a comparison of striatal DAT availability showed that subjects who dropped out of the detoxification program (most likely relapsed) had significantly lower DAT levels during the short abstinence period than those who completed detoxification. Methamphetamine abusers who dropped out performed worse in neuropsychological tests than those who did not. On follow-up, these subjects showed significant recovery of DAT levels, suggesting that low transporter levels after short-term abstinence may have reflected adaptive changes rather than irreversible neurotoxic effects. In contrast, there was only a trend for improvement in motor and cognitive functions, which did not reach significance, suggesting that the increase of DATs was not sufficient for complete recovery of function. Brain metabolism partially recovered after long-term abstinence.

Effort to find a possible alteration of receptor density in drug-abusing patients has perhaps tended to obscure other issues. Receptor number is just one of many components that determine neurochemical activity. The absence of change in DATs in chronic cocaine-abusing patients may reflect critical problems involved in studying static properties in a single neurotransmitter system. Furthermore, in methamphetamine abusers, DATs rebounded to normal levels, but cognition in these patients remained well below that of controls. This was

despite a return of DAT levels. Drug addiction, even cocaine addiction, is most likely not a single disease entity. Different stages of addiction related to different putative pathophysiological changes most likely exist. Changes found in isolated receptor systems in abusing populations may reflect an attempt to adapt to neurochemical abnormalities elsewhere. Clearly, variations in B_{max} and K_d occur in healthy nonabusing individuals [72] as well as in abusing patients, which would also impact their healthy capacity to adapt to internal and external stimuli. Measurements of dopaminergic function in response to a challenge might be more informative about the adaptive state of the neurotransmitter system (or different linked neurotransmitter systems) than about a single pathophysiological trait [78].

4.3. PET studies of nicotine abuse

In spite of the fact that there are 45 million cigarette smokers in the United States and there are 400,000 deaths/year associated with smoking, surprisingly, little is known about the neurochemical actions of tobacco smoke on the human brain. Imaging studies have been summarized in a recent book [79]. Nicotine stimulates nicotinic acetylcholine receptors, which in turn are thought to stimulate dopaminergic transmission [80]. The pharmacokinetics of inhaled nicotine has been measured using [^{11}C]nicotine [81], and acute administration of intravenous nicotine has been reported to reduce brain metabolism [82].

Recently, monoamine oxidase A (MAO A) and monoamine oxidase B (MAO B) have been examined in the human brain [83,84]. MAO breaks down neurotransmitter amines such as dopamine, serotonin and norepinephrine, as well as amines from exogenous sources. It occurs in two subtypes MAO A and MAO B, which can be imaged in vivo using [^{11}C]clorgyline and [^{11}C]L-deprenyl, respectively. It has been proposed that MAO is one of the molecular targets proposed to link smoking and depression [85,86] due to the antidepressant properties of MAO inhibitors. Since the antidepressant effects of nonselective MAO inhibitors are generally attributed to the inhibition of MAO A [87], it is possible that depressed smokers are self-medicating an overactive MAO A system. [^{11}C]L-deprenyl is a labeled version of the MAO B inhibitor drug L-deprenyl. Both clorgyline and L-deprenyl act through irreversible mechanisms, so when they are labeled with ^{11}C, they provide an opportunity to visualize enzymatic activity in vivo and to study the pharmacodynamics of MAO. PET studies indicate that smokers have a 28% reduction in MAO A [83] and a 40% reduction in MAO B relative to age-matched nonsmokers [84]. Since MAO inhibition is associated with enhanced activity of dopaminergic systems, this reduction may account for the reduced rate of Parkinson's disease in smokers [88]. Furthermore, these findings indicate that smoking-induced changes in MAO activity may also contribute to some of the features of smoking epidemiology, including high rates of smoking in people with psychiatric disorders such as depression and schizophrenia or polydrug abuse. There is evidence that smokers self-medicate in the case of certain psychiatric disorders and that they use smoking to reduce anxiety and to increase alertness and cognition [88,89].

Nicotine and smoking also provide an interesting problem with regard to dopamine-induced changes in [^{11}C]raclopride binding. In animals, nicotine itself produces mild but reproducible increases in extracellular dopamine (about 150–200%) [45,90–93]. PET studies have shown that these changes in extracellular dopamine are accompanied by a 5–12% displacement of [^{11}C]raclopride binding [91,94–96]. In an interesting series of studies, however, much larger tobacco-induced increases in dopamine (or decreases in [^{11}C]raclopride binding) were measured in smokers who were finally allowed to smoke during the scan and who had abstained for a period of time (up to 1 day) prior to the experiment [97,98]. These magnitudes of 26–37% decreases in [^{11}C]raclopride binding correlated with reported euphoric effects from smoking. Interestingly, this magnitude of change in [^{11}C]raclopride binding is similar to that found with cocaine-stimulated or amphetamine-stimulated dopamine release and emphasizes the importance of other facets of addiction, such as drug craving or subjective euphoria, in the dopaminergic response to these drugs.

Neurotransmitter receptor studies using PET and single-photon emission computed tomography have typically examined single neurotransmitter systems as if they function in isolation. It is unlikely that any psychiatric disease is attributed to isolated changes in a single neurotransmitter system, and drug addiction is no exception. Nevertheless, the critical role of the mesolimbic dopamine system appears to be a common denominator to the abuse liability of many drugs with very different molecular structures. Treatment, therefore, most likely resides in the aggressive targeting of those chemical systems that modulate dopamine. This also implies that potential treatments can focus on a common molecular target, as opposed to specialized treatments for each abused compound or behavior. This provides an attractive option to the pharmaceutical industry, which has long been hesitant to jump into the addiction treatment market, perhaps due to the misperception of unacceptably low profit margins or stigma [99].

5. Using PET to develop treatment for substance abuse

PET provides an ideal technique to probe a specific drug mechanism, and we have been able to use this technology to advance our understanding of fundamental changes in neural activity and structure that are associated with chronic drug abuse. However, the development and clinical implementation of an adequate therapy for addiction are not commensurate to our understanding of the neurochemical mechanisms of drugs of abuse. Given that prolonged exposure to drugs of abuse produces abnormalities in brain structure and function, potential pharmacotherapies that produce one response in the normal brain might produce quite another in an environment

altered by prolonged drug exposure. The observation that chronic drug abuse produces changes in the dynamics of the dopamine system has provided an impetus for the development of many strategies targeting this system to weaken the initial stimulatory effects of rewarding drugs [100]. It is possible that the most effective of these therapies might not act on dopaminergic systems directly but on systems functionally related to dopamine.

Studies in our laboratory [101,102] and those of others [51] have been exploring pharmacological interventions outside the dopaminergic system that might subsequently inhibit dopaminergic response to psychostimulants and other abused drugs. These studies are based on the premise that neurotransmitter systems do not work in isolation and that healthy brain function depends on the ability of the system to maintain a functional state of homeostasis across a network of interacting neurotransmitter systems. In this study, the inability of a specific neurotransmitter to be regulated by other etiologically relevant functionally linked systems underlies the characteristic addictive state of tolerance and insensitivity. This, then, is indicative of lack of plasticity or an inability to respond to previously stimulating doses of the addictive compound. For example, the diminished euphoria experienced by chronic cocaine abusers over time may be related to other factors such as the integrity of other neurotransmitter systems functionally linked to dopamine. Consequently, measuring the responsiveness of a specific neurotransmitter to a pharmacological challenge may be more revealing than measuring changes in more inherent static properties of these systems such as protein density.

Dopaminergic homeostasis is primarily maintained by the activity of excitatory amino acid (EAA) and inhibitory GABAergic systems [103]. Thus, these neurotransmitters become promising targets to alter the functional homeostasis of the dopamine system and, in this study, the responsivity of this system to a pharmacological perturbation. Under the hypothesis that either a priori diminishing EAA neurochemical stimulation of dopamine or augmenting inhibitory GABAergic control over dopamine will reduce reward-associated response to a drug challenge, our research team and others have been aggressively exploring the potential of these agents as therapies for drug abuse. However, while rodent and primate studies suggest that antagonizing EAA glutamate receptors directly may reduce dopaminergic response to drugs of abuse [104–106], glutamate receptor antagonists are known to produce psychosis [107]. The GABAergic system thus provides a more feasible approach to indirectly modulating dopaminergic response to drugs of abuse. Since PET provides the most clinically relevant technique to explore the effects of drugs of abuse, we have relied largely on PET data to guide further behavioral and in vivo techniques.

Our initial studies of the GABAergic modulation of dopamine activity focused on the interaction between the anticonvulsant drug ã-vinyl GABA (vigabatrin, GVG or Sabril) and dopaminergic response to psychostimulants [45,49,108–111]. Through irreversible inhibition of the enzyme responsible for the catabolism of GABA, GABA transaminase (GABA-T), GVG increases GABA concentrations in both vesicular and cytosolic pools [112]. Recent evidence suggests that the ability of GVG to increase cytosolic pools of GABA may contribute to its promise as a therapy for addiction. Drugs that depress dopaminergic function usually produce concomitant reductions in locomotor behavior [113]. However, recent studies suggest that increases in cytosolic pools of GABA produced by GVG are only released in response to abnormal stimulation of the dopaminergic system [114,115], such that normal locomotor activity and "natural" reinforcing events may be spared. This may explain findings suggesting that GVG does not diminish locomotor activity at clinically relevant doses [108,116,117]. Furthermore, because the mechanism of GVG is through irreversible inhibition, the time required between doses depends on the ability of the system to synthesize new stores of GABA-T, implying that minimal dosing schedules might provide prolonged protection of dopaminergic systems [118]. In this study, the potential for pharmacological tolerance within GABAergic systems is greatly reduced [119]. Moreover, rodent studies using prolonged GVG treatment have demonstrated no tolerance within related dopaminergic systems [120] (although see Neal and Shah [121]). In addition to these mechanistic advantages, increasing GABA activity as a general strategy has demonstrated remarkable success in both behavioral and neurochemical paradigms [122].

In as much as inhibiting dopaminergic response to abused drugs diminishes their addictive liability, PET studies are ideal for assessing the impact of potential therapies on dopaminergic response to psychostimulants or other abused drugs. This strategy is depicted in Fig. 4. The success of this PET-derived treatment has since been supported by many behavioral paradigms in animals demonstrating the potential of GVG as a pharmacotherapeutic agent for addiction. GVG reduces the effects of cocaine-induced brain reward stimulation [109] and cocaine self-administration [124] without affecting the reward associated with food [124] or water [116,125] intake. In addition, GVG reduces indices of craving for and drug-seeking behavior related to cocaine [111], nicotine [45] or heroin [126], as assessed by the CPP paradigm. Although animal models are typically designed to separate specific behavioral factors associated with a single drug-seeking or drug-taking behavior, little effort has been directed at developing animal models of polydrug use. However, evidence presented in Stromberg et al. [116] suggests that it is possible to develop a successful model of cocaine/alcohol abuse. The clinical relevance of this issue, described above along with the ability of GVG to modulate concurrent cocaine/alcohol intake [116], increases the promise of this strategy to treat drug abuse. Recently, two small open-label clinical trials using GVG were reported in both cocaine-dependent [127,128] and methamphetamine-dependent subjects [129]. The first trial was designed specifically to assess the utility of this treatment strategy

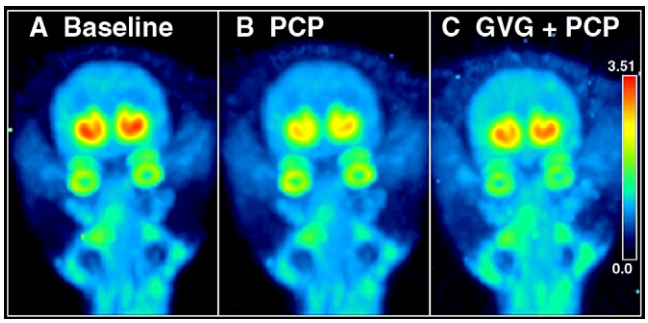

Fig. 4. Strategy for using PET to develop a treatment for substance abuse. GVG pretreatment blocks PCP-induced decreases in [^{11}C]raclopride binding. Volume-rendered parametric images of a *P. anubis* baboon undergoing a protocol identical to that used to assess the effects of addictive compounds on dopaminergic systems in humans. Decreases in [^{11}C] raclopride binding reflect increases in dopamine. (A) Baseline measurements give an assay of [^{11}C]raclopride bound to dopamine D_2 receptors not already occupied with dopamine. (B) Dopamine increases following PCP administration, decreasing [^{11}C]raclopride binding. (C) These decreases in [^{11}C]raclopride binding (increases in dopamine) are blocked by pretreatment with GVG. Parametric images are colored using an extended rainbow color scale (far right), where red represents image pixels with the highest DVR values. Data were taken from Schiffer et al. [123].

for cocaine dependence, while the second examined visual safety in a methamphetamine-dependent population. Both trials suggested clinical efficacy and demonstrated visual safety. Conclusive evidence for treatment efficacy must be obtained using a double-blind placebo-controlled approach. Those trials are currently ongoing.

6. Summary of findings and the status of treatment options

The above studies illustrate the use of PET in investigating the mechanisms of drugs of abuse and changes in brain chemistry that may account for the addictive actions of these drugs in the human brain. Although these studies remain preliminary, they have already documented neurochemical changes in the brains of individuals addicted to drugs and have provided a target for pharmacological intervention. Given the importance of radiotracer development in the advancement and application of neuroimaging techniques to the study of addiction, it is safe to say that basic research in labeling biomolecules with positron emitters has shaped the PET field as we know it today. Studies using ^{11}C-labeled compounds can thus make significant contributions to our awareness of many physiological and cognitive effects produced by chronic exposure to a number of different compounds (for review, see Refs. [71,130–132]). It is clear from studies presented above that PET has provided invaluable information on the addicted human brain that may be valuable for developing new treatment strategies for addiction.

Although experimental capabilities for more precisely delineating behavioral and biological mechanisms of drug reinforcement and addiction are generally at hand, the discipline remains largely at a descriptive stage of development. Much of its scientific literature attempts to ascertain whether a particular compound alters a particular class of behavior associated with compulsive drug taking or to assess self-administration produced by a potentially abused compound across a range of behavioral end points. Furthermore, little attempt may be made to rationalize the particular behavioral approach chosen, which may, instead, be based predominantly on an available apparatus or technology in that laboratory. Nonetheless, owing more to the sheer progression of studies within a laboratory, in certain areas, these studies have begun to provide the prerequisite foundation from which more mechanistic approaches can now proceed.

Perhaps one of the primary factors constraining both the scope and the advancement of drug abuse research may be the shortage of new radiotracers with sufficient specificity and appropriate kinetics to allow the study of molecular targets other than the handful dominating drug abuse research today. In many cases, research questions are framed around the availability of certain radiotracers rather than around a hypothesis based on current and emerging scientific knowledge. This might also be one of the factors contributing to the small number of brain targets implicated in human studies of a wide variety of abused drugs. The latter situation arises, no doubt at least in part, from limitations in radiotracer availability imposed by many factors, including the complexities of radiotracer synthesis with short-lived radioisotopes, which, in turn, are exacerbated by a shortage of trained chemists and lead compounds that can be labeled. In addition, once synthesized, radiotracers vary in their utility because of complex issues such as bioavailability, kinetics, specificity and metabolic stability. Every newly developed radiotracer requires extensive evaluation to determine the extent to which these variables impact its preclinical and clinical utility. Unfortunately, factors governing the interaction of chemical compounds (including radiotracers) with living systems are not well understood, and, thus, we cannot predict whether a newly synthesized radiotracer is going to be useful without actually performing preclinical and clinical studies. Clearly, addiction research will benefit from creative new thinking on how to both fast track radiotracer development in general and rapidly respond when new molecular targets are identified.

The majority of current imaging studies examining the effects of drug abuse on the brain have concentrated either on the involvement of dopamine systems in the reinforcing properties of these compounds or on morphological changes that might result from chronic abuse. Of growing concern, however, is the possibility that long-term drug exposure is accompanied by subclinical changes, which reflect a reduction in the adaptive capabilities of the nervous system. The ability to quantitate progressive changes in nervous system function during a time in which no observable signs of dysfunction are evident is an important consideration in the use of these imaging methods to study and stage recovery from drug abuse or addiction. In addition to providing

information regarding the time course of effects, repeated scanning of addicted individuals can also be used to operationally define appropriate time points or durations for intervention or rehabilitation. Functional PET images may be able to give an index of the vulnerability of dopamine systems to stimulatory effects of cocaine, cocaine craving or stress — subtle measures that may indicate prognosis or potential for long-term abstinence.

Finally, PET studies documenting the time course of recovery of brain dopamine systems following abstinence provide extremely useful information and should be made operational as soon as possible. A better base of communication and interfacing between science and government will accelerate progress in both fronts, allowing each to benefit from the other. Thus, scientific information such as that reviewed here, if disseminated properly and linked to the legislative process, can change the care and long-term prognosis of many addicted patients and their families in the immediate future.

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