Published in final edited form as:

Curr Top Behav Neurosci. 2010 ; 3: 199–217. doi:10.1007/7854_2009_24.

Imaging Receptor Changes in Human Drug Abusers

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Abstract

This chapter will review the literature on differences in the brain chemistry of alcohol- and drug-dependent individuals compared to healthy controls as measured with positron emission tomography and single photon emission computed tomography. Specifically, alterations in dopamine, serotonin, opioid, and GABA systems in cocaine, alcohol, nicotine, and heroin dependence have been examined. These neurochemical systems are integrated and play significant roles in a final common pathway mediating addiction in the brain. One recurrent finding is that dopaminergic dysfunction is prevalent in both alcohol and drug dependent populations, and specifically there is a lower availability of dopamine type 2/3 receptors in cocaine-, alcohol-, nicotine-, and heroin-dependent individuals compared to healthy controls. The development of novel radiotracers that target additional receptor systems will further our understanding of the neurochemical basis of addiction.

Keywords

Imaging; PET; SPECT; Drug abuse; Alcohol; Cocaine; Nicotine

1 Introduction

This chapter will briefly review the literature on differences in the brain chemistry of individuals with alcohol and drug dependence versus healthy, nondependent individuals in vivo as measured with positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging. Importantly, in humans we are not able to obtain “baseline” scans on drug dependent individuals from when they were drug-naïve; thus, data collected in drug abusers are typically compared to age-matched healthy controls. This means that we do not know whether the brain changes are pre-existing and represent a vulnerability to addiction, or whether they are a consequence to drug use. PET and SPECT receptor imaging is typically used to examine the neurochemistry of addiction during early detoxification and also during longer periods of withdrawal. The length of abstinence is an important variable to take into account in imaging studies, because different receptor systems have been shown to change during the recovery from drug and alcohol dependence, some in as little as several weeks; thus, length of abstinence will be noted when it is available. We cannot currently determine in humans whether differences in receptor or transporter availability are pre-existing or are a consequence; thus, this alternative conclusion is a caveat in all sections of this chapter. It is also important to note that many individuals with drug addiction also drink alcohol and/or smoke cigarettes, making it a complex process to determine which variable or combination of variables are contributing to the receptor changes. In the majority of studies, to date, smoking is not systematically controlled; thus, additional research will be required to untangle these relationships. PET and SPECT may also be used to measure striatal dopamine (DA) transmission, e.g., drug-induced changes in DA release, and this is covered in another chapter by Dr. Martinez. We

refer to receptor “availability” as opposed to receptor “levels” or “density” throughout the chapter to note that these studies are measuring receptors that are available to be bound by the radiotracer. This is because the radiotracer cannot bind to receptors that are already occupied, perhaps by the drug; e.g., cocaine, or an endogenous neurotransmitter such as dopamine. We are currently able to image a limited number of receptor systems in the brain; thus, the scope of this review is limited to existing radiotracers that are currently approved for use in humans.

2 Cocaine

2.1 Cocaine and the Dopamine Transporter

Cocaine acts directly at the DA transporter by blocking the reuptake of dopamine. Several studies report higher striatal DA transporter availability in acutely abstinent cocaine-dependent subjects compared to healthy controls using [^{123}I]beta-CIT SPECT (Jacobsen et al. 2000; Malison et al. 1998). Additionally, higher DA transporter availability was associated with worse scores on the Hamilton depression inventory (Malison et al. 1998). However, no difference in striatal DA transporter availability between chronic cocaine abusers (last use of cocaine was 5 ± 8 days) versus controls, but lower striatal DA transporter availability in detoxified cocaine abusers (last use 42 ± 7 days) was reported using [^{11}C]cocaine PET (Wang et al. 1997a). Differences in these studies are likely due to differences between the radiotracers [^{123}I]beta-CIT and [^{11}C]cocaine. Specifically, [^{11}C]cocaine is limited due to its low specific to nonspecific binding ratio and rapid clearance, and thus is more of a blood flow agent. It is also important to note that we do not know the half-life of cocaine in the brain; thus, while it rapidly clears in the blood it may remain in the brain for a longer period of time and interfere with radiotracer binding. A recent study using [$^{99\text{m}}\text{Tc}$]TRODAT, which labels striatal DA transporters, and SPECT also reported higher striatal DA transporter availability in recently abstinent (7.5 ± 9.7 days) cocaine dependent subjects vs. controls (Crits-Christoph et al. 2008). And, DA transporter levels tended to decrease with days since last use, suggesting that cocaine-induced increases in DA transporter availability may decrease during more prolonged abstinence. Because cocaine acts by blocking the reuptake of dopamine at the DA transporter, an increase in DA transporter availability suggests that chronic cocaine use induces a compensatory upregulation of the DA transporter. This is further supported by the data suggesting that when cocaine is removed, e.g., during prolonged abstinence, DA transporter availability decreases.

2.2 Cocaine and the D2/3 Receptor

There is a transient increase in DA levels in brain when cocaine blocks the DA transporter. The increase in DA levels is critical to cocaine's reinforcing effects, and thus cocaine-induced changes in DA receptor levels have been the subject of many studies (Table 1). For example, recently detoxified (within 1 week) cocaine abusers had lower striatal dopamine type 2/3 (D2/3) receptor availability measured with [^{18}F]N-methylspiroperidol PET (Volkow et al. 1990) compared to healthy controls. In the same study, cocaine abusers ($n = 3$) with 1 month of abstinence had similar striatal D2/3 receptor availability compared to controls (Volkow et al. 1990). A subsequent study, also using [^{18}F]N-methylspiroperidol PET, in a larger sample of cocaine abusers ($n = 20$) demonstrated lower striatal D2/3 receptor availability at 1 and 4 months of abstinence compared to healthy controls (Volkow et al. 1993), suggesting that the initial decrease in D2/3 receptor availability persists. These findings were further replicated using [^{11}C]raclopride PET. Specifically, chronic cocaine abusers had lower striatal D2/3 receptor availability during withdrawal, at approximately 2 weeks of abstinence (Martinez et al. 2004) and at 3–6 weeks of abstinence compared to healthy controls (Volkow et al. 1997). Taken together, these studies suggest that the striatal

dopamine system compensates for chronic cocaine use by decreasing the number of postsynaptic D2/3 receptors, and this decreased availability persists with prolonged abstinence. The ultimate effect in a chronic cocaine abuser is a dysregulated DA system which has important treatment implications; e.g., these individuals may be more resistant to treatment drugs that target DA neurotransmission. There does not appear to be a correlation between availability of D2/3 receptors and the reinforcing effects of cocaine in cocaine addiction. While high versus low striatal D2/3 receptor availability predicts unpleasant versus pleasurable experiences, respectively, to stimulants in healthy controls (Volkow et al. 1999, 2002a); this correlation was not replicated in cocaine-dependent individuals (Martinez et al. 2004).

Lower D2/3 receptor availability in dependent individuals compared to healthy controls has emerged as a consistent marker across all addictions. An alternative conclusion may be that addicted individuals have decreased D2/3 receptor availability prior to any drug use and that this represents vulnerability rather than consequence.

2.3 Cocaine and the Serotonin Transporter

While much of the work on the reinforcing and withdrawal effects of cocaine has focused on DA neurotransmission, serotonin (5-HT) dysfunction may also be involved since cocaine exhibits high affinity for the 5-HT transporter and increases 5-HT reuptake, which likely contributes to changes in mood associated with cocaine. Specifically, dopamine may be more involved in the locomotor activating effects and euphoric effects of cocaine, while serotonin may be important in the worsening mood that is reported during cocaine withdrawal. We can measure the 5-HT transporter in the diencephalon and brainstem with [123 I]beta-CIT and SPECT. Using this paradigm, Jacobsen et al. (2000) reported higher diencephalon and brainstem 5-HT transporter availability in smoked cocaine-dependent subjects during acute abstinence (e.g., 3.7 ± 3.8 days) compared to healthy controls. Higher 5-HT transporter availability is likely a compensatory upregulation to chronic cocaine use. Because the transporters remove extracellular serotonin, increased transporter availability may result in a decrease in synaptic serotonin levels, which may influence mood during acute withdrawal from cocaine. However, no correlations between transporter availability and measures of mood, impulsivity, or aggression were found (Jacobsen et al. 2000). Additional studies are needed to determine whether chronic cocaine use leads to changes in 5-HT transporters over more prolonged abstinence.

2.4 Cocaine and the mu-Opioid Receptor

The opioid system is widely implicated in the reinforcing effects of most drugs of abuse including cocaine. There are three opioid receptors (mu, delta, kappa) that are typically studied, and the mu-opioid receptor is known for modulating the positive reinforcing effects of drugs of abuse. [11 C]carfentanil PET has been used to measure mu-opioid receptor availability. In cocaine addicts during acute withdrawal (1–4 days), mu-opioid receptor availability was higher in the frontal and temporal cortices and anterior cingulate compared to healthy controls, and was positively correlated with the severity of craving on the day of the scan (Gorelick et al. 2005; Zubieta et al. 1996). Additionally, mu-opioid receptor availability increases over the first week of abstinence, remains elevated up to 4 weeks of abstinence, and begins to decrease to control levels by 12 weeks of abstinence (Gorelick et al. 2005; Zubieta et al. 1996). A recent study examined the relationship between mu-opioid receptor availability and time to relapse in cocaine users (Gorelick et al. 2008). Specifically, higher mu-opioid receptor availability at 1 and 12 weeks of abstinence in the frontal and temporal cortices was significantly associated with a shorter time to relapse. Put another way, the greater the decline in mu-opioid receptor availability during a 12-week abstinence period, the longer the time to relapse after discharge. These studies suggest that the mu-

opioid receptor plays a critical role in craving and relapse in cocaine users and may direct pharmacotherapies during abstinence and/or may provide a biochemical marker that helps identify individuals at high-risk of early relapse.

3 Alcohol

3.1 Alcohol and the D2/3 Receptor

Alcohol's rewarding effects are largely linked to the mesolimbic dopamine system (Vengeliene et al. 2008), and specifically, the D2/3 receptor plays a role in mediating the reinforcing effects of alcohol. As mentioned previously, [^{11}C]raclopride is widely used to examine the availability of D2/3 receptors. Here, the studies examining D2/3 receptor availability used [^{11}C]raclopride unless otherwise noted. Initial studies in this area indicated lower striatal D2/3 receptor availability in alcohol dependent subjects compared to controls (Hietala et al. 1994; Volkow et al. 1996a). Two additional studies by Dr. Heinz and colleagues found lower D2/3 receptor availability with [^{18}F]desmethoxyfallypride PET in alcohol-dependent subjects compared to controls (Heinz et al. 2004b, 2005b). And, two SPECT studies reported nonsignificantly lower D2/3 receptor availability in alcohol-dependent subjects compared to controls (Guardia et al. 2000; Repo et al. 1999). While many studies examine alcohol-dependence as a heterogeneous population, there is some evidence to subgroup alcohol dependence, specifically into Cloninger's Type I and II subtypes (Cloninger et al. 1988). Type I alcoholics are described as displaying a late-onset of alcoholism, (>25 years old), and they are initially more affected by the antianxiety effects of alcohol. Type II alcoholics typically have an early-onset of alcoholism (<25 years old), are more affected initially by the rewarding effects of alcohol, e.g., thrill seeking, and display antisocial and impulsive personality traits and also are characterized as having higher rates of criminal behavior. A preliminary study in Type II alcoholics found lower D2/3 receptor availability during early withdrawal, e.g., within 1 month, in the caudate and putamen, and lower availability in the caudate during late withdrawal, 1–4 months later (Volkow et al. 2002b) compared to controls, suggesting that changes in D2/3 receptor availability are initially lower and remain lower during prolonged withdrawal. An [^{123}I]epidepride SPECT study in Type I alcoholics with at least 1 week of abstinence (range 1 week to 4 years) found lower D2/3 receptor availability compared to controls in the left temporal pole (Kuikka et al. 2000). Thus, even when examining alcohol dependence by distinct subgroups, lower D2/3 receptor availability appears to be a consistent marker of alcohol dependence.

Several studies have examined the relationship between D2/3 availability and alcohol behaviors. Specifically, low availability of D2/3 receptors in ventral striatum was associated with a high level of craving and higher cue-induced (alcohol associated vs. control cue) brain activation in alcohol dependent subjects who had been abstinent on an average of 36 days (Heinz et al. 2004b). Additionally, low availability of D2/3 receptors was associated with a greater average daily amount of alcohol consumed, suggesting that low availability may be an indicator of greater severity of alcohol dependence (Martinez et al. 2005). These two studies suggest that low availability is associated with more marked severity of disease, e.g., increased consumption and increased craving. However, an interesting study used [^{123}I]iodobenzamide (IBZM) SPECT to correlate striatal D2/3 receptor availability during detoxification with treatment outcome at 3 months (Guardia et al. 2000). Alcohol dependent subjects who relapsed within 3 months had higher D2/3 receptor availability during detoxification compared to subjects who remained abstinent. This suggests that low DA levels or higher D2/3 receptor availability may indicate a vulnerability to early relapse. These studies generally support the hypothesis that alcohol dependence is linked to a dysregulation in dopamine neurotransmission.

3.2 Alcohol and the Dopamine Transporter

While alcohol does not act directly at the DA transporter, a dysfunction in the dopaminergic pathway as evidenced by reduced D2/3 receptor availability appears to extend to the DA transporter. Alcohol-dependent individuals have been reported to have lower (Laine et al. 1999; Repo et al. 1999) (Tiihonen et al. 1995), higher (Tiihonen et al. 1995) or similar (Volkow et al. 1996b) DA transporter availability compared to healthy controls (See Table 2). Volkow et al. (1996b) reported no difference in a small study of five alcohol-dependent individuals compared to controls using [^{11}C]d-threo methylphenidate PET. However, in a larger study of 27 alcohol-dependent individuals, there was lower DA transporter availability in human alcohol drinkers who were imaged with [^{123}I]beta-CIT and SPECT on admission for detoxification compared to healthy controls (Laine et al. 1999). Interestingly, these subjects were imaged again after 4 weeks of abstinence and there was an increase in DA transporter availability, which in some subjects approached or surpassed the level of DA transporter availability in control subjects (Laine et al. 1999). In a similar study, higher availability of DA transporters in alcoholics was associated with increased novelty seeking (Laine et al. 2001). Repo et al. (1999) found lower DA transporter availability in Type I alcoholics compared to controls, and Tiihonen et al. (1995) found lower versus higher DA transporter availability in nonviolent versus violent alcohol-dependent individuals, respectively, compared to controls. Thus, Type I alcoholics and nonviolent alcoholics tend to have lower DA transporter availability than controls. Conversely, two studies by Heinz and colleagues found no difference in DA transporter availability between alcohol-dependent individuals at 3–5 weeks of abstinence and healthy controls (Heinz et al. 1998, 2000). Many alcohol-dependent individuals also smoke cigarettes, although the majority of these studies did not control for tobacco smoking. Recently, it has been suggested that tobacco smoking may mediate the effects of alcohol at the DA transporter. Specifically, during acute abstinence, heavy drinkers had higher levels of DA transporters compared to nondrinkers and this effect was restricted to nonsmokers (Cosgrove et al. 2009b). This suggests that tobacco smoking suppresses alcohol-induced increases in DA transporters during early withdrawal. Additional studies specifically designed to assess the effects of tobacco smoking in more severe alcohol dependence need to be performed.

3.3 Alcohol and the Serotonin Transporter

A large preclinical literature links serotonergic dysfunction along with specific genetic and social/environmental interactions to alcohol dependence (Wrase et al. 2006). Because serotonin is critically tied to mood regulation, it is thought that dysregulated serotonin in alcohol dependence may be tied to negative mood states including depression and anxiety which are highly comorbid with alcohol dependence. 5-HT transporter availability has been reported to be lower (Heinz et al. 1998; Szabo et al. 2004) and similar (Brown et al. 2007) in recent and long-term abstinent alcoholics compared to controls. Specifically, lower midbrain and brain-stem 5-HT transporter availability was found in 22 alcohol-dependent men after 3–5 weeks with [^{123}I]beta-CIT SPECT (Heinz et al. 1998) and at least 2 years* of abstinence* (n = 15) with [^{11}C]McN5652 and PET (Szabo et al. 2004) compared to healthy controls, which was correlated with depression and anxiety during withdrawal (Heinz et al. 1998). A more recent study reported no difference in 5-HT transporter availability between 30 alcoholics who were abstinent on an average of 14 days, and 18 healthy controls using [^{11}C]DASB PET (Brown et al. 2007), which is a more selective ligand for 5-HT transporters than [^{123}I]beta-CIT. There are some limitations to [^{123}I]beta-CIT SPECT measurement of 5-HT transporter availability. For example, the radiotracer may be influenced by endogenous 5-HT (Heinz et al. 2004a) and/or there may be difficulties in quantification due to the low signal in the neocortex (Kuikka et al. 1995; vanDyck et al. 2000). However, the majority of these studies did not control for tobacco smoking. A recent study suggests that heavy drinkers have higher 5-HT transporters than nondrinkers, and this difference is mediated by

tobacco smoking. Specifically, heavy drinker nonsmokers had significantly higher 5-HT transporters compared to nondrinker nonsmokers, but heavy drinker smokers had similar 5-HT transporter levels compared to nondrinker smokers (Cosgrove et al. 2009b). Additionally, there was a significant positive correlation between diencephalon and brainstem 5-HT transporter availability and days since last drink, suggesting that during acute withdrawal, there is a compensatory increase in 5-HT transporters in nonsmokers but not smokers. This suggests that smoking suppresses the alcohol-induced increase in 5-HT transporter availability over the first week of abstinence. Thus, the serotonin transporter may be involved in mediating the effects of drinking and smoking on serotonergic tone during acute alcohol withdrawal.

3.4 Alcohol and the mu-Opioid Receptor

The opioid system is responsible for modulating reward to natural reinforcers such as food and also to drugs of abuse including alcohol. The endogenous opioid system is made up of mu-, delta-, and kappa-opioid receptors, which are modulated by the endogenous opioid peptides enkephalin, beta-endorphin, and dynorphin. Agonists at the mu-opioid receptor stimulate the mesolimbic dopamine system and are rewarding. Alcohol indirectly interacts with the opioid receptor by increasing endogenous levels of beta-endorphin and enkephalin, which bind the mu-opioid receptor. Much of the research has focused on the mu-opioid receptor, which can be measured in vivo with [^{11}C]carfentanil PET. Two studies to date have examined mu-opioid receptor availability in alcohol dependent subjects. In the first study, 25 alcohol dependent subjects at 1–3 weeks of abstinence had higher mu-opioid receptor availability in the ventral striatum, including the nucleus accumbens, compared to healthy controls which was positively correlated with alcohol craving (Heinz et al. 2005a). Interestingly, a subset of these alcohol dependent subjects remained abstinent and was scanned again 5 weeks later, and their mu-opioid receptor availability remained elevated, suggesting this elevation is long lasting. In the second study, eight alcohol dependent subjects scanned at 4 days of abstinence exhibited lower mu-opioid receptor availability in the right dorsal lateral prefrontal cortex, the right anterior frontal cortex and the right parietal cortex compared to healthy controls (Bencherif et al. 2004). They did not examine the nucleus accumbens. Additionally, they report that lower mu-opioid receptor availability was correlated with higher craving in these areas. While more research needs to be done in this area to determine changes in the availability of mu-opioid receptors in the recovery from alcohol dependence, these studies highlight the role of the mu-opioid receptor in alcohol craving during acute abstinence. This is consistent with the use of naltrexone, a mu-opioid antagonist, as an anticraving drug in the treatment of alcoholism.

3.5 Alcohol and the GABA_A-BZ Receptor

GABA receptors are ligand gated ion channels that are the primary mechanism for modulating inhibitory synaptic transmission in the brain, and it is well established that GABA_A receptors have a central role in modulating the effects of ethanol in the central nervous system (Davies 2003; Kumar et al. 2004). Alterations in GABAergic neurotransmission are strongly associated with symptoms of alcohol tolerance, dependence, and withdrawal, and thus the GABA_A receptor has been a target of neuroimaging research. The GABA_A-benzodiazepine receptor (GABA_A-BZR) can be measured with [^{123}I]iomazenil SPECT or [^{11}C]flumazenil PET. These two radiotracers have comparable quantitation in vivo (Bremner et al. 1999). SPECT studies have demonstrated *lower* GABA_A-BZR availability in alcohol dependent subjects at approximately 1 month (Abi-Dargham et al. 1994), 3 months (Lingford-Hughes et al. 1998, 2000), and 7 months (range of 2–18 months) (Lingford-Hughes et al. 2005) of alcohol withdrawal, and *similar* GABA_A-BZR availability in alcohol-dependent subjects at approximately 3 weeks of withdrawal vs. controls (Litton et al. 1993). However, the most recent study, which was the first to evaluate

GABA_A-BZRs while controlling for tobacco smoking status, demonstrated *higher* availability of GABA_A-BZRs at about 1 week withdrawal in alcohol-dependent nonsmokers that was suppressed in alcohol-dependent smokers, suggesting that tobacco smoke suppressed the alcohol-induced increase in GABA_A-BZR availability (Staley et al. 2005). Additionally, this elevation was correlated with more severe alcohol withdrawal symptoms in alcohol-dependent nonsmokers, which were not apparent in alcohol-dependent smokers, suggesting that tobacco smoking may block some symptoms of alcohol withdrawal by suppressing the increased availability of GABA_A-BZR during acute withdrawal from alcohol. At 4 weeks of abstinence the higher GABA_A-BZR availability in alcohol-dependent nonsmokers had decreased and was similar to the alcohol-dependent smokers and controls suggesting a normalization of the receptor over time (Staley et al. 2005). These findings have several implications. One, they suggest that GABA_A-BZR availability undergoes a compensatory increase during early recovery from alcohol dependence and decreases during prolonged withdrawal. Two, the changes over time are mediated by tobacco smoking, which has important clinical implications. If the nicotine in tobacco smoke is responsible for suppressing the alcohol-induced increase in GABA_A-BZRs and suppressing some of the associated alcohol withdrawal symptoms, it suggests that smokers who desire to quit smoking and drinking when they enter treatment may benefit from nicotine replacement therapy to help cope with both nicotine and alcohol withdrawal symptoms.

4 Nicotine

4.1 Nicotine and the β_2^* -Nicotinic Acetylcholine Receptor (β_2^* -nAChR)

Nicotine, the primary addictive ingredient in tobacco smoke, acts at the nicotinic acetylcholine receptor (nAChR) and exerts its reinforcing effects at nAChRs containing the β_2^* -subunit* (β_2^* -nAChR). It is well known from preclinical and postmortem studies that chronic nicotine and tobacco smoking upregulate β_2^* -nAChRs and this has recently been confirmed in vivo. Specifically, there is a higher availability of β_2^* -nAChRs in tobacco smokers during acute abstinence compared to never smokers in the cerebellum, striatum, and throughout the cortex (Mukhin et al. 2008; Staley et al. 2006). Additionally, this upregulation, or higher availability, is temporary (Mamede et al. 2007) and in most people decreases to nonsmoker levels between 6 and 12 weeks of abstinence from tobacco smoking (Cosgrove et al. 2009a) (See Fig. 1). Studies are ongoing to determine variables that may affect individual differences in the regulation of the β_2^* -nAChR during prolonged abstinence. Individual differences in the rate of normalization during prolonged abstinence may have individual-specific treatment indications. For example, if a faster rate of normalization is associated with increased craving, those individuals may benefit from nicotine replacement therapy, which may slow the normalization of the receptor and decrease craving.

4.2 Nicotine and the D1 Receptor

The dopamine type 1 (D1) receptor is important in tobacco smoking due to its involvement in the mesolimbic reward pathway and because it has been implicated in cognition. The cognitive impairments and deficits that some smokers report during withdrawal make this an important area of research. However, to date, only one study has evaluated differences in D1 receptor availability between smokers and nonsmokers. Tobacco smokers had significantly lower D1 receptor availability compared to nonsmokers measured with [¹¹C]SCH 23390 and PET (Dagher et al. 2001). This difference was most profound in the ventral striatum. This suggests that the dopaminergic system may be underactive in smokers, and thus may promote continued tobacco smoking. It is also possible that because chronic tobacco smoking results in sustained dopamine and other neurotransmitter release by both nicotine and monoamine oxidase inhibitors, which are in tobacco smoke, there is a resulting

downregulation of D1 receptor. Future studies should address whether D1 receptor availability changes over time during withdrawal from tobacco smoking and whether it is correlated with changes in cognition.

4.3 Nicotine and the D2/3 Receptor

The D2/3 receptor is critical to the rewarding effects of all drugs of abuse. Several studies have examined differences in D2/3 availability between tobacco smokers and nonsmokers. Two studies have reported no difference in striatal D2/3 receptor availability between actively smoking tobacco smokers and nonsmokers using [^{123}I]IBZM and SPECT (Yang et al. 2006, 2008). In a subsequent larger study, tobacco smokers had significantly lower D2/3 receptor availability in the bilateral putamen while actively smoking and 24 h after smoking cessation compared to never smokers using [^{11}F]fallypride PET (Fehr et al. 2008). Additionally, D2/3 receptor availability correlated positively with craving in the ventral striatum, and negatively in the anterior cingulate and inferior temporal cortex. Differences between the studies may be due to the higher resolution of PET, differences between radiotracers, and/or because the tobacco smokers in Fehr et al. (2008) smoked for more years than in Yang et al. (2006). This finding of decreased D2/3 receptor availability in tobacco smokers compared to controls is consistent with findings of lower D2/3 receptor availability in individuals dependent on cocaine, alcohol and heroin as discussed earlier in this chapter. This suggests that dopamine D2/3 dysfunction is pervasive in addiction in general, and not specific to a particular class of drugs.

4.4 Nicotine and the Dopamine Transporter

The dopamine transporter is responsible for regulating dopamine levels in the synapse. Since tobacco smoking increases dopamine release, we might expect that chronic tobacco smoking would lead to changes in dopamine transporter numbers. One initial study showed no difference between smokers and nonsmokers in striatal DA transporter availability with [^{123}I]beta-CIT and SPECT (Staley et al. 2001). However, two recent studies using [$^{99\text{m}}\text{Tc}$]TRODAT and SPECT, report significantly lower striatal DA transporter availability in smokers vs. nonsmokers (Newberg et al. 2007; Yang et al. 2008). The lower DA transporter availability in smokers is likely a downregulation in response to tobacco smoking-induced increases in synaptic DA. Lower DA transporter availability was associated with increased severity of nicotine dependence as measured by the Fagerström Test for Nicotine Dependence (Yang et al. 2008), further suggesting that heavier smoking, which may lead to increased dopamine release results in greater downregulation of the DA transporter.

4.5 Nicotine and the Serotonin Transporter

Tobacco smoking results in the release of a cascade of neurotransmitters including serotonin. This may lead to adaptations in the serotonin transporter, which is responsible for removal of serotonin from the synapse. Only one study using [^{123}I]beta-CIT and SPECT has examined potential differences in 5-HT transporter availability between smokers and nonsmokers (Staley et al. 2001). The study found modestly higher 5-HT transporter availability in men smokers compared to nonsmokers in the brainstem (10%), but not in the diencephalon. This provides some evidence that smoking may regulate the 5-HT transporter in men, but additional studies with more selective radiotracers are needed to confirm this finding. This finding is important because the serotonin system is responsible for mood regulation and a poor mood during tobacco smoking withdrawal is a primary reason tobacco smokers are unable to successfully quit smoking.

5 Opiates

5.1 Opiate Dependence and the mu-Opioid Receptor

The mu-opioid receptor has been widely studied because it is critical for the rewarding properties of many drugs of abuse, especially opiate addiction. In a preliminary study, men who were dependent on heroin, but recently detoxified ($n = 3$), e.g., 1 week, had higher mu-opioid receptor availability measured with [^{11}C]carfentanil PET in the inferofrontal cortex and anterior cingulate compared to healthy controls ($n = 3$) (Zubieta et al. 2000). This is likely due to an upregulation of the mu-opioid receptors in response to chronic heroin use, which may be implicated in the tolerance to the rewarding effects that is reported by heroin users. Additional studies are needed to determine receptor changes during prolonged withdrawal.

5.2 Opiate Dependence and the D2/3 Receptor

Very few studies have been conducted on receptor availability in heroin and/or opiate-dependent subjects in large part because of the physical withdrawal symptoms associated with imaging them acutely after their last drug administration. As previously discussed, the D2/3 receptor is a critical reward substrate and low D2/3 receptor availability may represent a vulnerability to addiction or a consequence of chronic use. Two studies found that opiate-dependent men had significantly lower striatal D2/3 receptor availability compared to controls using [^{123}I]IBZM SPECT (Zijlstra et al. 2008) and [^{11}C]raclopride (Wang et al. 1997b). Additionally, Zijlstra et al. (2008) reported that lower striatal D2/3 availability was associated with more years of opiate and polydrug use, suggesting that the lower D2/3 availability is tied to the chronicity of drug use in general. This suggests that low D2/3 receptor availability and dopaminergic dysfunction is more likely a consequence of chronic drug use.

6 Conclusions

In this chapter, we have reviewed differences in the brain chemistry of drug- and alcohol-dependent individuals compared to healthy controls. Cocaine dependence is associated with a higher availability of DA and 5-HT transporters and mu-opioid receptors during acute abstinence compared to healthy controls. The higher DA transporter and mu-opioid receptor availability tends to decrease over prolonged abstinence from cocaine. Alcohol dependence is associated with higher GABA_A-BZR availability compared to controls during acute abstinence that decreases with prolonged abstinence. Additionally, the alcohol-induced changes in GABA_A-BZR and DA and 5-HT transporter availability appear to be modulated by comorbid tobacco smoking. Importantly, the rates of comorbidity of substance dependence with tobacco smoking and other drugs of abuse are high and additional studies that systematically examine these variables are needed. Less research has been conducted on tobacco smoking and heroin dependence. One consistent finding is that tobacco smokers have higher beta₂*-nAChR availability than nonsmokers which decreases with prolonged abstinence. A main theme throughout this chapter has been a lower availability of D2/3 receptors in drug-dependent individuals compared to healthy controls. This is true for cocaine, alcohol, nicotine, and heroin and thus suggests that low D2/3 availability is a hallmark feature of drug dependence. It is still not clear, however, whether this predates the drug use, and thus confers a vulnerability, or whether it is a consequence of chronic drug consumption. Additionally, the polydrug issue should not be overlooked. While it is still highly likely that low D2/3 is a marker for vulnerability to become dependent on each of these drugs, it has not been ruled out that this effect is primarily due to comorbid tobacco smoking or alcohol consumption.

The neurochemical systems outlined in this review that are involved in addiction are likely integrated and play significant roles in a final common pathway mediating addiction in the brain. While we can currently image only a handful of chemical sites in the brain, the recent explosion in radiotracer development will ultimately increase our understanding of addiction in the living human brain.

Acknowledgments

This work was supported by National Institute of Health grants RO1 DA015577, KO2 DA21863, KO1 DA20651, P50 DA13334, and P50 AA15632.

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Abbreviations

PET Positron emission tomography

SPECT	Single Photon emission computed tomography
DA	Dopamine
5-HT	Serotonin
GABA_A-BZR	GABA _A -benzodiazepine receptor
β₂*-nAChR	β ₂ *-subtype of the nicotinic acetylcholine receptor
D1	Dopamine type 1 receptor
D2/3	Dopamine type 2/3 receptor

Fig. 1.

Reprinted with permission from *Archives of General Psychiatry* (2009), 66, 672. These are mean parametric images in transaxial view illustrating β_2^* -nAChR availability in nonsmokers and smokers during acute and prolonged abstinence. Measurements for the smokers were obtained at 1 day and 1, 2, 4, and 6–12 weeks of abstinence. The color scale is shown with red, yellow, green, and blue corresponding to values of β_2^* -nAChR availability (V_T/f_p). Note the higher β_2^* -nAChR availability in the striatum, cerebellum and cortex in the smokers at 1 week of abstinence compared to the nonsmokers which decreases over time

Table 1
Studies examining D2/3 receptor availability in cocaine dependence compared to controls

Radiotracer	Time abstinent	Main finding	Reference
[¹⁸ F] <i>N</i> -methylspiroperidol	1 week	Lower availability	Volkow et al. (1990)
[¹⁸ F] <i>N</i> -methylspiroperidol	1 month	Similar availability	Volkow et al. (1990)
[¹⁸ F] <i>N</i> -methylspiroperidol	1 and 4 months	Lower availability	Volkow et al. (1993)
[¹¹ C]raclopride	2 weeks	Lower availability	Martinez et al. (2004)
[¹¹ C]raclopride	3–6 weeks	Lower availability	Volkow et al. (1997)

¹¹C and ¹⁸F radioisotopes are used with PET

Table 2
Studies examining DA transporter availability in alcohol dependence compared to controls

Radiotracer	Time abstinent	Main finding	Reference
[¹²³ I]beta-CIT	4–8 weeks	Lower availability/nonviolent	Tiihonen et al. (1995)
[¹²³ I]beta-CIT	4–8 weeks	Higher availability/violent	Tiihonen et al. (1995)
[11C]-d-threomethylphenidate	52 ± 48 days	Similar availability	Volkow et al. (1996b)
[¹²³ I]beta-CIT	1–4 days	Lower availability	Laine et al. (1999)
[¹²³ I]beta-CIT	4 weeks	Similar availability	Laine et al. (1999)
[¹²³ I]PE2I	7–165 days	Lower availability/type I	Repo et al. (1999)
[¹²³ I]beta-CIT	3–5 weeks	Similar availability	Heinz et al. (1998)
[¹²³ I]beta-CIT	3–5 weeks	Similar availability	Heinz et al. (2000)
[¹²³ I]beta-CIT	1–5 days	Higher availability/nonsmokers	Cosgrove et al. (2009a, b)
[¹²³ I]beta-CIT	1–2 days	Similar availability/smokers	Cosgrove et al. (2009a, b)

¹¹C radioisotopes are used with PET, ¹²³I radioisotopes are used for SPECT