Addiction, a Disease of Compulsion and Drive: Involvement of the Orbitofrontal Cortex

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Understanding the changes in the brain which occur in the transition from normal to addictive behavior has major implications in public health. Here we postulate that while reward circuits (nucleus accumbens, amygdala), which have been central to theories of drug addiction, may be crucial to initiate drug self-administration, the addictive state also involves disruption of circuits involved with compulsive behaviors and with drive. We postulate that intermittent dopaminergic activation of reward circuits secondary to drug self-administration leads to dysfunction of the orbitofrontal cortex via the striato-thalamo-orbitofrontal circuit. This is supported by imaging studies showing that in drug abusers studied during protracted withdrawal, the orbitofrontal cortex is hypoactive in proportion to the levels of dopamine D2 receptors in the striatum. In contrast, when drug abusers are tested shortly after last cocaine use or during drug-induced craving, the orbitofrontal cortex is hypermetabolic in proportion to the intensity of the craving. Because the orbitofrontal cortex is involved with drive and with compulsive repetitive behaviors, its abnormal activation in the addicted subject could explain why compulsive drug self-administration occurs even with tolerance to the pleasurable drug effects and in the presence of adverse reactions. This model implies that pleasure *per se* is not enough to maintain compulsive drug administration in the drug-addicted subject and that drugs that could interfere with the activation of the striato-thalamo-orbitofrontal circuit could be beneficial in the treatment of drug addiction.

Research on drug addiction has focused on the mechanism underlying the reinforcing effects of drugs of abuse. This research has led to the identification of neuronal circuits and neurotransmitters involved with drug reinforcement. Of particular relevance to drug reinforcement is the dopamine (DA) system. It has been postulated that the ability of drugs of abuse to increase DA in limbic brain regions (nucleus accumbens, amygdala) is crucial for their reinforcing effects (Koob and Bloom, 1988; Pontieri *et al.*, 1996). However, the role of DA in drug addiction is much less clear. Also, while the reinforcing effects of drugs of abuse may explain the initial drug-taking behavior, reinforcement *per se* is insufficient in explaining the compulsive drug intake and the loss of control in the addicted subject. In fact, self-administration of drugs occurs even when there is tolerance to the pleasurable responses (Fischman *et al.*, 1985) and sometimes even in the presence of adverse drug effects (Koob and Bloom, 1988). It has been postulated that drug addiction is the result of changes in the DA system and in the reward circuits involved in drug reinforcement secondary to chronic drug administration (Dackis and Gold, 1985; Epping-Jordan *et al.*, 1998). However, it is also possible that brain circuits other than those regulating the pleasurable responses to drugs of abuse are involved with drug addiction.

In analyzing which circuit(s) other than those involved with reward processes are involved with addiction it is important to realize that the key symptoms of drug addiction in humans are compulsive drug intake and the intense drive to take the drug at the expense of other behaviors (American Psychiatric Association, 1994). We therefore postulate that circuits involved with drive and perseverative behaviors are involved with drug addiction. More specifically we postulate that intermittent DA stimulation secondary to chronic drug use leads to disruption of the orbitofrontal cortex via the striato-thalamo-orbitofrontal circuit, which is a circuit involved in regulating drive (Stuss and Benson, 1986). The dysfunction of this circuit results in the compulsive behavior in addicted subjects and the exaggerated motivation to procure and administer the drug regardless of its adverse consequences. This hypothesis is corroborated by imaging studies showing disruption of striatal, thalamic and orbitofrontal brain regions in drug abusers (Volkow *et al.*, 1996a). This review summarizes those studies concentrating primarily in the orbitofrontal cortex and on studies of cocaine and alcohol addiction. This review also provides a brief description of the anatomy, function and pathology of the orbitofrontal cortex that is relevant to addiction and proposes a new model of drug addiction that invokes both conscious (craving, loss of control, drug preoccupation) and unconscious processes (conditioned expectation, compulsivity, impulsivity, obsessiveness) which result from dysfunction of the striato-thalamo-orbitofrontal circuit.

Anatomy and Function of the Orbitofrontal Cortex Relevant to Addiction

The orbitofrontal cortex is an area that is neuronatomicaly connected with brain areas known to be involved with the reinforcing effects of drugs of abuse. More specifically, the nucleus accumbens, which is considered to be the target for the reinforcing effects of drugs of abuse (Koob and Bloom, 1988; Pontieri *et al.*, 1996), projects to the orbitofrontal cortex via the mediodorsal nucleus of the thalamus (Ray and Price, 1993). In turn, the orbitofrontal cortex provides dense projections to the nucleus accumbens (Haber *et al.*, 1995). The orbitofrontal cortex also receives direct projections from DA cells in the ventral tegmental area (Oades and Halliday, 1987), which is the DA nucleus associated with drug reinforcing effects (Koob and Bloom, 1988). In addition, the orbitofrontal cortex also receives direct and indirect (via thalamus) projections from other limbic brain regions known to be involved with drug reinforcement, such as amygdala, cingulate gyrus and hippocampus (Ray and Price, 1993; Carmichael *et al.*, 1995). This makes the orbitofrontal cortex not only a direct target for the effects of drugs of abuse but also a region that could integrate information from various limbic areas and, because of its reciprocal connections, a region that in turn could also modulate the response of these limbic brain regions to drug administration (Fig. 1).

Among the various functions of the orbitofrontal cortex, its role in reward-related behaviors are of most relevance when

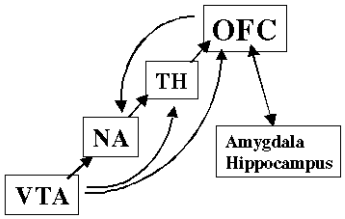

Figure 1. Neuroanatomic diagram of the connections of the orbitofrontal cortex that are pertinent for drug reinforcement and addiction. VTA = ventral tegmental area, NA = nucleus accumbens, TH = thalamus, OFC = orbitofrontal cortex.

analyzing its potential involvement in drug addiction. To start with, in laboratory animals placement of stimulation electrodes into the orbitofrontal cortex readily induces self-stimulation (Phillips *et al.*, 1979). These effects appear to be modulated by DA since they are blocked by the administration of DA receptor antagonists (Phillips *et al.*, 1979). It is also well recognized that the orbitofrontal cortex, in addition to processing information about the rewarding properties of stimuli (Aou *et al.*, 1983; Tremblay and Schulz, 1999), is also involved in modifying an animal's behavior when the reinforcing characteristics of these stimuli change (Thorpe *et al.*, 1983) and in learning stimulus–reinforcement associations (Rolls, 1996; Schoenbaum *et al.*, 1998). Though these functions have been characterized for physiological reinforcers such as food (Aou *et al.*, 1983), it is likely that they subserve a similar role for pharmacological reinforcers.

In laboratory animals damage of the orbital frontal cortex results in impairment of reversal of stimulus–reinforcement associations, and leads to perseveration and resistance to extinction of reward-associated behaviors (Butter *et al.*, 1963; Johnson, 1971). This is reminiscent of what happens to drug addicts who frequently claim that once they start taking the drug they cannot stop even when the drug is no longer pleasurable.

Another function of relevance for this review is the involvement of the orbitofrontal cortex in motivational states (Tucker *et al.*, 1995). Because it is believed that striato-cortical circuits are important in the inhibition of common responses in contexts in which they are not adequate (Marsden and Obeso, 1994), the dysfunction of the striato-thalamo-orbitofrontal circuit secondary to chronic drug use could participate in the inappropriately intense motivation to procure and self-administer the drug in addicted subjects.

However, very few animal studies have directly investigated the role of the orbitofrontal cortex in drug reinforcement. This subject is covered in greater detail elsewhere (Porrino and Lyons, 2000). Here we want to note that these studies implicate the orbitofrontal cortex on the conditioned responses that drugs of abuse elicit. For example, rats exposed to an environment in which they had previously received cocaine showed activation of the orbitofrontal cortex but not the nucleus accumbens (Brown *et al.*, 1992). Also rats with lesions of the orbital frontal cortex do not show cocaine-conditioned place preference (Isaac *et al.*, 1989). Similarly lesions of the thalamic mediodorsal nucleus (including the paraventricular nucleus) have been shown to disrupt conditioned reinforced behaviors (Mc Alona *et al.*, 1993; Young and Deutch, 1998) and to attenuate cocaine self-administration (Weissenborn *et al.*, 1998). This is relevant because conditioned responses induced by drugs of abuse have been implicated in the craving elicited in humans by exposure to stimuli associated with the drug administration (i.e stress, money, syringes, street) (O'Brien *et al.*, 1998). This craving response, in turn, is one of the factors that contributes to relapse in drug abusers (McKay, 1999).

We also want to note that in DA transporter knockout mice, self-administration of cocaine results in activation of the orbitofrontal cortex (Rocha *et al.*, 1998). This latter finding is particularly intriguing in that in these animals drug self-administration was not associated with activation of the nucleus accumbens, which is recognized as the target for the reinforcing effects of drugs of abuse. Thus this study suggests the importance of the orbitofrontal cortex in maintaining drug self-administration under conditions in which the nucleus accumbens is not necessarily activated.

Though not for drug-related stimuli, imaging studies in human subjects have also corroborated the involvement of the orbitofrontal cortex in reinforced behaviors and in conditioned responses. For example, activation of the orbitofrontal cortex in human subjects has been reported when performance in a cognitive task is associated with monetary reward but not when it is not (Thut *et al.*, 1997), and also when expecting a conditioned stimulus (Hugdahl *et al.*, 1995).

Orbitofrontal Cortex Pathology in Human Subjects

In humans, pathology in the orbitofrontal cortex and striatum has been reported in patients with obsessive compulsive disorders (Baxter *et al.*, 1987; Modell *et al.*, 1989; Insel, 1992), which share with addiction the compulsive quality of the behavior. Moreover, in patients with Tourette's syndrome, obsessions, compulsions and impulsivity, all of which are behaviors present in drug addiction, were found to be associated with increases in metabolic activity in the orbitofrontal cortex and striatum (Braun *et al.*, 1995). Also a recent case report on a patient with a vascular lesion of the orbitofrontal cortex describes a syndrome of compulsive illegal car borrowing that led to frequent incarceration and that was described by the subject as inducing a pleasurable relief (Cohen *et al.*, 1999).

Of interest for this review are also reports implicating the thalamus with compulsive behaviors. Noteworthy are clinical case studies describing compulsive self-stimulation in patients with stimulating electrodes implanted in the thalamus (Schmidt *et al.*, 1981; Portenoy *et al.*, 1986). The compulsive self-stimulation in these patients was described as reminiscent of the compulsive drug self-administration seen in addicted subjects.

Imaging Studies in Substance Abusers

Most of the imaging studies involved with addiction have used positron emission tomography (PET) in conjunction with 2-deoxy-2-[^{18}F]fluoro-D-glucose, an analog of glucose, to measure regional brain glucose metabolism. Because brain glucose metabolism serves as an indicator of brain function, this strategy allows mapping of the brain regions that change as a function of drug administration or of drug withdrawal and enables the identification of any correspondences between changes in regional brain function and symptoms in drug abusers. However, various molecular targets involved in DA neurotransmission and that of other neurotransmitters, such as receptors, transporters and enzymes, have also been investigated. The relatively low radiation dose from the positron emitters has allowed the measurement of more than one molecular target in a given subject.

Activity of the Orbitofrontal Cortex during Detoxification

Studies assessing changes at different times after detoxification have been carried out on cocaine abusers and alcoholic subjects. In the case of cocaine abusers, these studies have shown that during early withdrawal (within 1 week of last cocaine use) metabolism in the orbitofrontal cortex and striatum was significantly higher than that in controls (Volkow *et al.*, 1991). The metabolism in the orbitofrontal cortex was significantly correlated with the intensity of the craving; the higher the metabolism, the more intense the craving.

In contrast, cocaine abusers studied during protracted withdrawal had significant reductions in several frontal regions, including the orbitofrontal cortex and anterior cingulate gyrus, when compared with non-abusing controls (Volkow *et al.*, 1992). These decreases persisted even when subjects were re-tested 3–4 months after the initial detoxification period.

Dopamine and the Activity of Orbitofrontal Cortex

To test if the disruptions in activity of the orbitofrontal cortex and anterior cingulate gyrus in the detoxified cocaine abusers were due to changes in DA brain activity, we examined the relationship between changes in DA D2 receptors and changes in regional metabolism. When compared with controls, cocaine abusers (within 1 month of last cocaine use) showed significantly lower DA D2 receptor levels in the striatum and these reductions persisted 3–4 months after detoxification. Decreases in striatal D2 receptor levels were associated with decreased metabolism in the orbitofrontal cortex and in the anterior cingulate gyrus (Volkow *et al.*, 1993a). Subjects with the lowest levels of D_2 receptors showed the lowest metabolic values in these brain regions (Fig. 2).

The association of metabolism in the orbitofrontal cortex and cingulate gyrus with striatal DA D2 receptors was interpreted as reflecting either an indirect regulation by DA of these regions via striato-thalamo-cortical projections (Nauta, 1979; Heimer *et al.*, 1985; Haber, 1986) or the cortical regulation of striatal DA D2 receptors via cortico-striatal pathways (Le Moal and Simon, 1991). The former case would imply a primary defect in DA pathways whereas the latter would imply a primary defect in the orbitofrontal cortex and in the cingulate gyrus in cocaine abusers.

Because the reductions in metabolism in the orbitofrontal cortex and cingulate gyrus in cocaine abusers were correlated with D2 receptor levels it was of interest to assess if increasing synaptic DA activity could reverse these metabolic changes. For this purpose a study was done that evaluated the effects of DA increases (achieved by the administration of the psychostimulant drug methylphenidate) on regional brain glucose metabolism in detoxified cocaine abusers. Methylphenidate (MP) increased metabolism in the anterior cingulate gyrus,

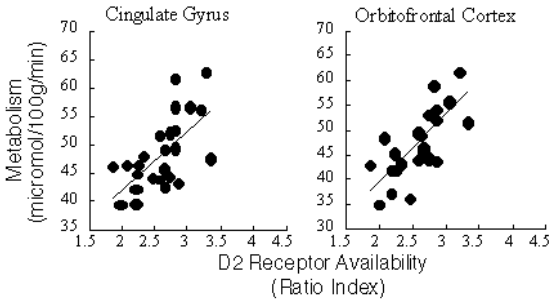

Figure 2. Relationship between regional brain glucose metabolism in cingulate gyrus ($r = 0.64$, df 24, $P < 0.0005$) and orbitofrontal cortex ($r = 0.71$, df 24, $P < 0.0001$) and dopamine D2 receptor availability (Ratio Index) in the striatum in detoxified cocaine abusers.

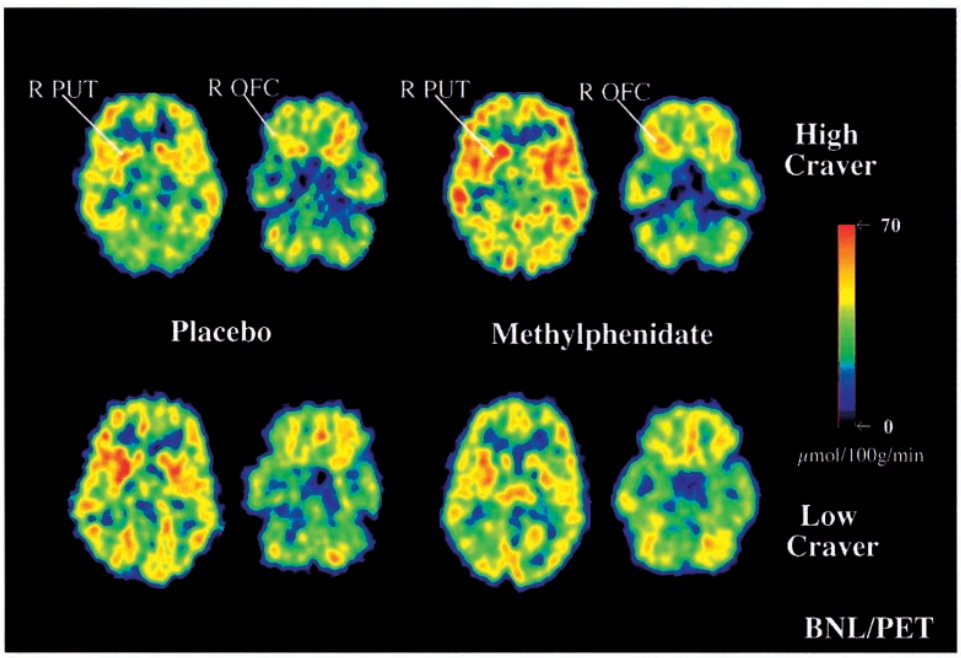

Figure 3. Regional brain metabolic images of a cocaine abuser in whom methylphenidate induced intense craving and one in whom it did not. Notice the activation of the right orbitofrontal cortex (R OFC) and of the right putamen (R PUT) in the subject reporting intense craving.

right thalamus and cerebellum. In addition, in cocaine abusers in whom MP induced significant levels of craving (but not in those in whom it did not) MP increased metabolism in the right orbitofrontal cortex and right striatum (Fig. 3).

The increase in metabolic activity in the cingulate gyrus after MP administration suggests that its hypometabolism in cocaine abusers reflects in part decreased DA activation. In contrast, MP only increased metabolism in the orbitofrontal cortex in those subjects in whom it enhanced craving. This would suggest that hypometabolic activity of the orbitofrontal cortex in the detoxified cocaine abusers is likely to involve disruption of other neurotransmitters apart from DA (i.e glutamate, serotonin, GABA). This would also suggest that while DA enhancement may be necessary it is not sufficient by itself to activate the orbitofrontal cortex.

Since the orbitofrontal cortex is involved with the perception of salience of reinforcing stimuli, the differential activation of the orbitofrontal cortex in subjects that reported intense craving could reflect its participation as a function of the perceived reinforcing effects of MP. However, because orbitofrontal cortex activation has also been linked with expectation of a stimulus (Hugdahl *et al.*, 1995), its activation in subjects in whom MP induced craving could reflect the expectation in these subjects of receiving another dose of MP. Moreover, the activation of a circuit that signals an expected reward may be consciously perceived as craving. That the correlation with craving was also observed in the striatum most likely reflects its neuroanatomical connections with the orbitofrontal cortex via the striato-thalamo-orbitofrontal circuit (Johnson *et al.*, 1968).

Activation of the orbitofrontal cortex by MP, a drug pharmacologically similar to cocaine (Volkow *et al.*, 1995), may be one of the mechanisms by which cocaine elicits craving and the subsequent compulsive drug administration in the addicted subject.

The Orbitofrontal Cortex and Cocaine Craving

Hyperactivity of the orbitofrontal cortex appears to be associated with self-reports of cocaine craving. This was noted, as described in the previous sections, in cocaine abusers tested shortly after last use of cocaine and when MP administration resulted in an increase in the intensity of the craving.

Activation of the orbitofrontal cortex has also been demonstrated in studies that were designed to assess the brain regions that became activated during exposure to stimuli designed to elicit cocaine craving. For one study cocaine craving was elicited by a cocaine theme interview (preparation of cocaine for self-administration). Regional brain glucose metabolism during the cocaine theme interview was compared with that during a neutral theme interview (family genogram). The cocaine theme interview significantly increased metabolism in the orbitofrontal cortex and left insular cortex when compared with the neutral theme interview (Wang *et al.*, 1999). Increased metabolism of the orbitofrontal cortex in addition to activation in the amygdala, prefrontal cortex and cerebellum was also reported in a study that used a videotape of cocaine scenes designed to elicit craving (Grant *et al.*, 1996). However, a study that measured changes in cerebral blood flow (CBF) in response to a videotape of cocaine reported activation of the cingulate gyrus and the amygdala but not of the orbitofrontal cortex during craving (Childress *et al.*, 1999). The reason for this failure to detect activation of the orbitofrontal cortex is unclear.

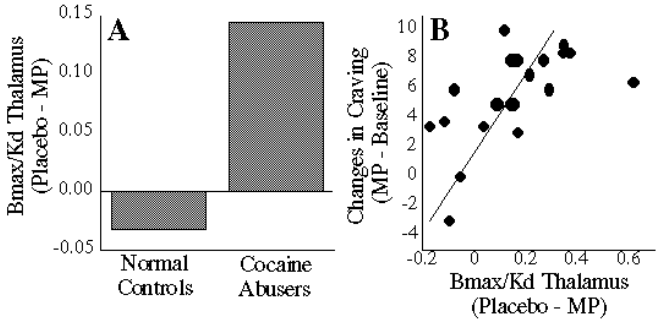

Figure 4. (*A*) Effects of methylphenidate (MP) on binding of [^{11}C]raclopride in thalamus (B_{max}/K_d) in controls and in cocaine abusers. (*B*) Relationship between MP-induced changes in B_{max}/K_d in thalamus and MP-induced changes in self-reports of craving in the cocaine abusers ($r = 61$, df, 19, $P < 0.005$).

Dopamine Stimulation, the Thalamus and Cocaine Craving

Changes in DA concentration in the human brain can be tested with PET using [^{11}C]raclopride, a ligand whose binding to the DA D2 receptor is sensitive to competition with endogenous DA (Ross and Jackson, 1989; Seeman *et al.*, 1989; Dewey *et al.*, 1992). This is done by measuring changes in the binding of [^{11}C]raclopride induced by pharmacological interventions (i.e. MP, amphetamine, cocaine). Because [^{11}C]raclopride binding is highly reproducible (Nordstrom *et al.*, 1992; Volkow *et al.*, 1993b) these reductions primarily reflect changes in synaptic DA in response to the drug. Note that for the case of MP, which increases DA by blocking the DA transporter (Ferris *et al.*, 1972), the changes in DA are a function not only of the levels of transporter blockade but also of the amount of DA that is released. If similar levels of DA transporter blockade are induced across two groups of subjects, then differences in the binding of [^{11}C]raclopride are mostly due to differences in the release of DA. Using this strategy it has been shown that with aging there is a decrease in striatal DA release in healthy human subjects (Volkow *et al.*, 1994).

Comparison of the responses to MP between cocaine abusers and controls revealed that MP-induced decrements in [^{11}C]raclopride binding in the striatum in the cocaine abusers were less than half of that seen in the controls (Volkow *et al.*, 1997a). In contrast, in the cocaine abusers, but not in the controls, MP significantly decreased binding of [^{11}C]raclopride in the thalamus (Fig. 4a). MP-induced decreases in [^{11}C]raclopride binding in the thalamus, but not in the striatum, were associated with MP-induced increases in self-reports of craving (Fig. 4b). This was intriguing since DA innervation of the thalamus is mainly limited to the mediodorsal and paraventricular nuclei, which are relay nuclei to the orbitofrontal cortex and cingulate gyrus respectively (Groenewegen, 1988), and since there is significant binding of cocaine and MP in the thalamus (Wang *et al.*, 1993; Madras and Kaufman, 1994). It was also intriguing in that the normal controls did not show a response in the thalamus, which if anything would point to an abnormally enhanced thalamic DA pathway in the addicted subjects. Thus, one could speculate that in the addicted subject abnormal activation of the DA thalamic pathway (presumably mediodorsal nucleus) could be one of the mechanisms that enables the activation of the orbitofrontal cortex.

Summary of Imaging Studies in Cocaine Abusers

Imaging studies have provided evidence of abnormalities in the striatum, thalamus and orbitofrontal cortex in cocaine abusers.

In the striatum, cocaine abusers show both a decrease in the levels of DA D2 receptors as well as a blunted release of DA. In the thalamus, cocaine abusers show an enhanced responsivity of the DA thalamic pathway. In the orbitofrontal cortex, cocaine abusers show hyperactivity shortly after the last use of cocaine and also during experimentally induced drug craving and hypoactivity during withdrawal, which is associated with reductions in striatal DA D2 receptors. We speculate that the striatal reduction in DA release and in DA D2 receptors results in a decreased activation of reward circuits that leads to hypoactivity of the cingulate gyrus and may contribute to that of the orbitofrontal cortex.

Imaging Studies in Alcoholism

Activity of the Orbitofrontal Cortex during Detoxification

Multiple studies have been carried out to assess metabolic changes in alcoholic subjects during detoxification. Most studies have consistently shown a reduction in frontal metabolism, including the anterior cingulate gyrus and orbitofrontal cortex, in alcoholic subjects. Though studies have shown a significant recovery on the baseline measures of metabolism with alcohol detoxification, when compared with controls, alcoholics still had significantly lower metabolism in orbitofrontal cortex and in anterior cingulate gyrus (Volkow *et al.*, 1997b). Similarly studies performed with single photon emission computed tomography have shown significant decreases in CBF in orbitofrontal cortex in alcoholics subjects during detoxification (Catafau *et al.*, 1999). The fact that the orbitofrontal cortex changes were present 2–3 months after detoxification (Volkow *et al.*, 1997b) indicates that they are not a function of withdrawal from alcohol but represent longer lasting changes. Moreover, the fact that in rats repeated intoxication with alcohol leads to neuronal degeneration in the orbital frontal cortex (Corso *et al.*, 1998) brings up the possibility that the persistent hypometabolism in the orbitofrontal cortex in the alcoholics may reflect alcohol's neurotoxic effects.

Dopamine and the Activity of the Orbitofrontal Cortex

Disruption of the striato-thalamo-orbitofrontal has also been proposed to participate in the craving and loss of control in alcoholism (Modell *et al.*, 1990). While PET studies have documented significant reductions in DA D2 receptors in alcoholics when compared with controls (Volkow *et al.*, 1996b), no study has been done to determine if there is a relation between the decrements in D2 receptors and the changes in metabolic activity in the orbitofrontal cortex in alcoholic subjects.

Though DA is of relevance in the reinforcing effects of alcohol (El-Ghundi *et al.*, 1998), its effects in other neurotransmitters (opiates, NMDA, serotonin, GABA) have also been implicated in its reinforcing and addictive effects (Lewis, 1996).

GABA and the Activity of the Orbitofrontal Cortex

The effect of alcohol on GABA neurotransmission is of particular interest in that at the doses abused by humans, alcohol facilitates GABA neurotransmission. It has also been hypothesized that alcohol addiction is the result of decreased GABA brain function (Coffman and Petty, 1985). However, it is unclear how changes in GABA brain function could contribute to addictive behaviors in alcoholic subjects. PET has been used to study the brain GABA system by measuring the regional brain metabolic changes induced by an acute challenge with a benzodiazepine drug – since benzodiazepines, like alcohol, also facilitate GABA neurotransmission in brain (Hunt, 1983) – and by directly measuring the concentration of benzodiazepine receptors in the human brain.

The regional brain metabolic response to lorazepam in recently detoxified alcoholic subjects has been compared with that in healthy controls. Lorazepan decreases whole-brain glucose metabolism to the same extent in normal and alcoholic subjects (Volkow *et al.*, 1993c). However, alcoholic subjects showed significantly less of a response than controls in thalamus, striatum and orbitofrontal cortex. These findings were interpreted as reflecting a decreased sensitivity to inhibitory neurotransmission in the striato-thalamo-orbitofrontal circuit in alcoholics during early detoxification (2–4 weeks after last alcohol use). A subsequent study assessed the extent to which these blunted responses normalized with protracted detoxification. This study showed that even after protracted detoxification (8–10 weeks after detoxification) alcoholics had a blunted response in the orbitofrontal cortex when compared with controls (Volkow *et al.*, 1997b). This suggests that the hyporesponsivity of the orbitofrontal cortex is not just a function of alcohol withdrawal but could reflect a regionally specific decrease in sensitivity to inhibitory neurotransmission in alcoholics.

Further evidence of the involvement of GABA in the long-lasting functional changes in the orbitofrontal cortex of alcoholics is also provided by a study that measured levels of benzodiazepine receptors in the brains of detoxified alcohol abusers (>3 months detoxification) using [^{123}I]Iomazenil. This study showed that detoxified alcoholics had significant reductions in the levels of benzodiazepine receptors in the orbitofrontal cortex when compared with controls (Lingford-Hughes *et al.*, 1998). A reduction in the levels of benzodiazepine receptors in the orbitofrontal cortex could explain the blunted regional brain metabolic responses to lorazepam administration in this brain region in the alcoholic subjects. One could postulate that a consequence of the reduced sensitivity to GABA neurotransmission could be a defect in the ability of inhibitory signals to terminate the activation of the orbitofrontal cortex in these subjects.

Serotonin and the Activity of the Orbitofrontal Cortex

The orbitofrontal cortex receives significant serotonergic innervation (Dringenberg and Vanderwolf, 1997) and thus serotonin abnormalities could also contribute to the abnormal function of this brain region. Evidence that this may be the case was provided by a study that measured changes in regional brain metabolism in response to m-chlorophenylpiperazine (mCPP), a mixed serotonin agonist/antagonist drug, in alcoholics and controls. This study showed that mCPP-induced activation in thalamus, orbitofrontal cortex, caudate and middle frontal gyrus was significantly blunted in alcoholics when compared with controls (Hommer *et al.*, 1997). This was interpreted as reflecting a hyporesponsive striato-thalamo-orbitofrontal circuit in alcoholics. The abnormal response to mCPP suggests an involvement of the serotonin system in the abnormalities seen in this circuit in alcoholic patients. In support of this is a study showing reductions in serotonin transporters, which serve as markers for the serotonin terminals, in the mesencephalon of alcoholic subjects (Heinz *et al.*, 1998). In this respect it is also interesting to note that serotonin reuptake inhibitor drugs have

been shown to be effective in decreasing alcohol intake in alcoholic subjects (Balldin *et al.*, 1994).

Summary of Imaging Studies in Alcoholics

Imaging studies have provided evidence of abnormalities in the striatum, thalamus and orbitofrontal cortex in alcoholics. In the striatum, thalamus and orbitofrontal cortex alcoholics have a blunted regional brain metabolic response to either GABAergic or serotonergic stimulation suggestive of hyporesponsiveness in this circuit. In addition detoxified alcoholics also showed decreases in metabolism, flow and benzodiazepine receptors in the orbitofrontal cortex. These abnormalities are therefore likely to reflect in part changes in GABAergic and serotonergic activity.

Drug Addiction as a Disease of Drive and Compulsive Behavior

Here we postulate that repeated exposure to drugs of abuse disrupts the function of the striato-thalamo-orbitofrontal circuit. As a consequence of this dysfunction a conditioned response occurs when the addicted subject is exposed to the drug and/or drug-related stimuli that activates this circuit and results in the intense drive to get the drug (consciously perceived as craving) and compulsive self-administration of the drug (consciously perceived as loss of control). This model of addiction postulates that the drug-induced perception of pleasure is particularly important for the initial stage of drug self-administration but that with chronic administration pleasure *per se* cannot account for the compulsive drug intake. Rather, dysfunction of the striato-thalamo-orbitofrontal circuit, which is known to be involved with perseverative behaviors, accounts for the compulsive intake. We postulate that the pleasurable response is required to form the conditioned association for the drug to elicit an activation of the orbitofrontal cortex on subsequent exposure. The orbitofrontal cortex, once activated, will cause what is consciously perceived as an intense urge or drive to take the drug even when the subject may have conflicting cognitive signals telling him/her not to do it. Once he/she takes the drug the DA activation that ensues during the intoxication maintains the activation of the striato-thalamo-orbitofrontal circuit, which sets a pattern of activation that results in perseveration of the behavior (drug administration) and which is consciously perceived as loss of control. An analogy that may be useful to explain the dissociation of pleasure from drug intake in the addicted subject could be that occurring during prolonged food deprivation when a subject will eat any food regardless of its taste, even when it is repulsive. Under these circumstances the urge to eat is not driven by the pleasure of the food but by the intense drive from the hunger. It would therefore appear that during addiction the chronic drug administration has resulted in brain changes that are perceived as a state of urgency not dissimilar to that observed on states of severe food or water deprivation. However, different from a state of physiological urgency for which the execution of the behavior will result in satiation and termination of the behavior, in the case of the addicted subject the disruption of the orbitofrontal cortex coupled with the increases in DA elicited by the administration of the drug set a pattern of compulsive drug intake that is not terminated by satiety and/or competing stimuli.

During withdrawal and without drug stimulation, the striato-thalamo-orbitofrontal circuit becomes hypofunctional, resulting in a decrease drive for goal-motivated behaviors. The pattern of derangements in activity in this circuit, hypoactive when there is no drug and/or drug-related stimuli and hyperactive during intoxication, is similar to the derangement seen with epilepsy, which is characterized by an increase in activity of the abnormal foci during the ictal period and by decreased activity during the interictal state (Saha *et al.*, 1994). The long-lasting abnormalities in the orbitofrontal cortex could lead one to predict that reactivation of compulsive drug intake could occur even after prolonged periods of drug abstinence as a result of activation of rewards circuits (nucleus accumbens, amygdala) by exposure either to the drug or to drug-conditioned stimuli. In fact studies in laboratory animals have shown re-instatement of compulsive drug intake after protracted drug withdrawal upon re-exposure to the drug (Ahmed and Koob, 1998).

An interesting question that results from this model is the extent to which the abnormalities in the orbitofrontal cortex are specific to disruptions related to drug intake or whether they result in other compulsive behaviors. Though there is not much data on the prevalence of other compulsive behaviors in addicted subjects, there is some evidence from studies that substance abusers report having higher scores in Compulsive Personality scales than non-drug abusers (Yeager *et al.*, 1992). Moreover studies have shown that in pathological gambling, which is another disorder of compulsive behavior, there is an association with high alcohol and/or drug abuse (Ramirez *et al.*, 1983).

This model of addiction has therapeutic implications for it would imply that drugs that could either decrease the threshold for its activation or increase the threshold for its inhibition could be therapeutically beneficial. In this respect it is interesting that the anticonvulsant drug gamma vinyl GABA (GVG), which decreases neuronal excitability by increasing GABA concentration in brain, has been shown to be effective in blocking drug self-administration and place preference irrespective of the drug of abuse tested (Dewey *et al.*, 1998, 1999). Though the ability of GVG to block drug-induced increases in DA in the nucleus accumbens has been postulated to be responsible for its efficacy in inhibiting conditioned place preference and self-administration, here we postulate that GVG's ability to decrease neuronal excitability may also be involved via its interference with the activation of the striato-thalamo-orbitofrontal circuit. Also, because the striato-thalamo-orbitofrontal circuit is regulated by multiple neurotransmitters (Modell *et al.*, 1990), non-dopaminergic drugs that modulate this pathway could also be beneficial in treating drug addiction. In this respect it is interesting to note that drugs that increase serotonin concentration in the brain decrease cocaine self-administration (Glowa *et al.*, 1997) whereas procedures that decrease serotonin increase breaking points for cocaine administration (Loh and Roberts, 1990), a finding which was interpreted as serotonin interfering with the drive for drug self-administration.

Though imaging studies seem to implicate the striato-thalamo-orbitofrontal circuit in drug addiction, other brain regions, such as the anterior cingulate gyrus, medial temporal structures (amygdala and hippocampus) and insular cortex, also appear to be involved. While imaging studies have identified the orbitofrontal cortex in addiction, more research is needed to identify the areas within the orbitofrontal cortex and the thalamus that are involved.

Notes

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