BNL-61771

BRAIN IMAGING STUDIES OF THE COCAINE ADDICT: IMPLICATIONS FOR REINFORCEMENT AND ADDICTION

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INTRODUCTION

Cocaine's highly reinforcing and addictive properties are manifested to the extreme in laboratory animals who, given free access of cocaine, will self-administer until death[1]. This sets cocaine apart from other drugs of abuse which are not self-administered at the expense of life-prolonging and life-preserving behaviors. Animal studies have shown that the brain dopamine (DA) systems appear central to cocaine's reinforcing and addictive properties[2-7].

Studies in humans evaluating the effects of chronic cocaine on dopamine brain function have been marked by inconsistencies. Because of the inaccesability of the human brain to investigation until recently theses studies had been limited to the evaluation of indirect parameters of dopamine activity and to measurements in postmortetm brains. Studies measuring prolactin and growth hormone as indirect indices of central DA activity have reported increases[8-11] as well as no changes[12-14] in cocaine abusers. Studies on plasma HVA concentration in cocaine abusers have also been unsuccessful in delineating a consistent pattern of abnormalities[14-16]. Postmortem studies have reported decreased brain DA concentration[17,18] decreases[19] and increases[20] in DA transporter sites; decreases in mRNA's for D_2 receptors[21] and decreases in D_1 receptors[22] in cocaine abusers. Pharmacological studies report findings suggestive of decreased and/or abnormal function of DA receptors in cocaine abusers: blunted response to DA agonists[23,24] and increased sensitivity to DA antagonists[25-27].

With Positron Emission Tomography (PET), an imaging method used to track the regional distribution and kinetics of chemical compounds labeled with short-lived positron-emitting isotopes in the living body[28] it is now possible to directly evaluate the involvement of the dopamine system in the addictive and reinforcing properties of cocaine in human subjects. Different elements from the DA synapse have been investigated with PET. The presynaptic element (DA neurons) has been investigated using tracers to measure DA metabolism, DA transporter sites and vesicular transporters[29]. The postsynaptic elements have been investigated with tracers that measure DA D2 and DA D1 receptor availability. There are currently no specific PET ligands to differentially evaluate DA D3, D4, and D5 receptors. The use of 2-deoxy-2-[18F]-fluoro-D-glucose (FDG) has made it possible to measure regional brain glucose metabolism in brain areas neuroanatomically connected with the DA systems. Since positron emitters can be used to label compounds without affecting their pharmacological behaviour PET can be used to measure cocaine's pharmacokinetics and binding pattern in DA neurons in the human brain[29].

PET has been used to evaluate the effects of acute cocaine on brain glucose metabolism[30] and the effects of chronic cocaine on cerebral blood flow[31], glucose metabolism during early[32] and late[33] cocaine withdrawal, DA metabolism[34], and DA D_2 receptor availability[35], as well as the pharmacokinetics and distribution of cocaine[29] and cocaethylene (a metabolite from cocaine and ethanol) in the human brain[36] with and without alcohol intoxication[37] and the distribution of 11C cocaine in the human body[38]. This chapter summarizes studies which evaluate different components of the DA system in cocaine abusers and the consequences of these changes in brain function and their relation to addictive behaviours. The studies for the various DA variables are first described separatedly according to the diagram in figure 1 after which the correlational studies are described. This chapter also summarizes studies on cocaine pharmacokinetics since they are of relevance in understanding the uniquely reinforcing properties of cocaine.

DOPAMINE D2 RECEPTOR AVAILABILITY

Dopamine D_2 receptor availability was measured using ^{18}F-N-methylspiroperidol (NMS) in cocaine abusers (n= 7) tested within one week of last cocaine use[35]. The PET scans were performed with the PET VI tomograph in the high-resolution mode (in-plane resolution of 9 mm, full width half maximum (FWHM)). Dynamic scans were obtained after injection of 4-6 mCi 18F NMS for a total of 4 hours. Values for DA D_2 receptor availability were obtained using the ratio

index (RI)[39]. Values for the RI were significantly lower in cocaine abusers (2.6 ±0.67) than in normal controls (3.98±0.92) (t=3.2; p≤0.01)(figure2). Values of DA receptor availability as obtained with Patlak's graphical analyses[40] revealed a significantly lower Ki value for cocaine abusers (0.081±0.04) than for normal controls (0.122±0.02) (t=2.7; p≤0.05). Three cocaine abusers tested 2 weeks after last cocaine use showed values for D2 availability similar to those of normal controls.

To evaluate if these changes were temporary or long lasting a second study was done in another group of 20 cocaine abusers who were tested 1-7 weeks after last use of cocaine and were compared with a group of 20 normal controls[41]. Different from the previous study the cocaine abusers were inpatients and were maintained in the hospital to ensure absence of psychoactive substances. The studies were done on a whole-body, high-resolution positron emission tomograph (6.5mm x 5.9mm Full Width Half Maximum at the center of the field of view, interslice distance 5.9mm, 15 slices, Computer Technologies, Incorporated, CTI 931). .Dynamic scans were obtained after injection of 4-6 mCi 18FNMS for a total of 3 hours. Values of DA D_2 receptor availability as measured with 18F NMS and the ratio index for cocaine abusers (2.65±0.46) were significantly lower than those obtained in normals (3.08±0.45) (t=2.9; p≤0.01) (Figure 3). Values of DA receptor availability as obtained with Patlak's graphical analyses revealed a significantly lower Ki value for cocaine abusers (0.093±0.02) than for normal controls (0.119±0.02) (t=3.2; p≤0.005). On the 7 subjects who remained in the rehabilitation program showed values of RI similar to those shown initially (Initial RI 2.5±0.4; RI after 3 months of detoxification 2.6±0.3) (figure 4).

For both the normals (N) and the cocaine abusers (C), the RI decreased as a function of age (N r=0.72 p ≤0.0005; C r=0.58 p ≤0.01). DA receptor availability and the Beck Depression Inventory were negatively correlated (r=-0.70 p ≤0.001) (Fig 4). There was no correlation found between DA receptor availability in these group of detoxified cociane abusers, and cocaine craving (figure 5)

PRESYNAPTIC DOPAMINE TERMINALS

Because ^{11}C-cocaine in the basal ganglia has been shown to bind predominantly to the DA transporter[29] this ligand was used to evaluate the presynaptic DA terminals. These results summarize data in 15 cocaine abusers and 12 normal controls[42]. There were no differences in pharmacokinetics or in metabolism of ^{11}C-cocaine between normals[42]. The uptake of ^{11}C-cocaine in basal ganglia was decreased in cocaine abusers when compared with normals as measured with the K1 obtained using Logan plots[43]. K1 values corresponded to 0.521 in normal controls and 0.403 in cocaine abusers ($p < 0.01$). Measurement of the distribution volume and index of binding site availability was also decreased in cocaine abusers when compared with normal controls (distribution volume for ^{11}C cocaine in basal ganglia were for N=4.82 ± 18 and for C=3.25 ± 0.645 ml/min; t=3.43 p ≤ 0.01). Decreased ^{11}C cocaine binding in basal ganglia could represent either downregulation of the DA transporter or degeneration of presynaptic DA terminals. However, because ^{11}C-cocaine binding was also lower in thalamus and cerebellum, we cannot exclude the possibility that the decreased binding could reflect decreased cerebral blood flow (CBF), decreases in binding sites other than the DA transporter and/or decreases in non-specific binding. Therefore, the extent to which PDN are affected in cocaine abusers is still unclear and requires further investigation.

A preliminary evaluation of DA metabolism with ^{18}F L-Dopa reported decreased uptake of this tracer in cocaine abusers (n=2)[34].

REGIONAL BRAIN GLUCOSE METABOLISM

It has been postulated that cocaine addiction is the result of depletion of brain DA secondary to chronic cocaine administration[9]. However, studies evaluating the effects of chronic cocaine administration on the DA system have yielded contradictory results[44] and the use of DA agonists

has not been successful in the long-term treatment of the cocaine addict[12]. The inconsistencies in results and the discrepancies among investigators could reflect, in part, the role of the DA system as a regulator of brain regions that subserve addictive behaviors as opposed to these behaviors being encoded in the DA system itself[45]. Thus, the effects of chronic cocaine on brain DA could lead to addiction through its consequences on the brain regions that it modulates. Alternatively, abnormalities in these brain regions prior to drug exposure could be associated with a higher vulnerability for drug addiction. In order to asses if projection areas of the DA system were involved in the addictive behaviour in cocaine abusers we used FDG to evaluate regional brain glucose metabolism both in projection areas of the nigrostriatal and of the mesocortical dopamine system. Because brain glucose metabolism reflects brain activity[45,13], its measurement in conjunction with that of specific neurotransmitter ligands enables an assessment of their functional significance. Furthermore because these studies are carried out directly in human subjects it allows to link neurochemical and metabolic brain changes with the clinical symptomatology.

Because cocaine withdrawal and detoxification may entail changes in dopaminergic activity we evaluated patients both during early[32] and late cocaine withdrawal[33]. During early cocaine withdrawal (<1 week), cocaine abusers (n=10) showed significantly higher metabolism in orbito-frontal cortex (OFC) and basal ganglia than cocaine abusers tested 1-4 weeks after detoxification (n=5) and that of normal controls (n=15) (figure 6). The metabolic activity in these brain regions was significantly correlated with the days since last cocaine use and after 1 week of detoxification cocaine abusers did not show this hypermetabolic pattern.

Metabolic activity in OFC ($r = 0.63$ $p < 0.02$) and prefrontal cortex ($r = 0.70$ $p < 0.003$) were significantly correlated with intensity of cocaine craving (figure 7).

A second study was done in a group of 20 cocaine abusers tested 1-7 weeks after last use of cocaine and were compared with 24 normal controls[33]. Cocaine abusers were maintained in the hospital to control for drug use. Global cerebral glucose metabolism was not significantly different between controls and cocaine abusers (N=38.4±3, C=36.5±5 μmol/100 g min, NS). However, metabolism in the frontal cortical areas, was significantly lower in cocaine abusers. The cocaine abusers had significantly ($p < 0.05$) lower metabolic activity in 16 of the 21 left frontal regions and 8 of the 21 right frontal regions. The decrease in frontal metabolism persisted after 3-4 months of detoxification.

Normalization of regional brain glucose metabolic measures by whole brain metabolism to assess if the decreases in frontal metabolism were persisted after accounting for global brain metabolism. These relative measures showd significant diminution in frontal metabolism which persisted 3 months after detoxification. In contrast relative decreases in parietal metabolism demonstrated during the first 7 weeks of detoxification were no longer evident 3 months later (figure 8).

Frontal metabolism was negatively correlated with the dose of cocaine used ($r=-0.47$, $p\leq0.01$) and with the years of use ($r=-.42$, $p\leq0.05$). Interestingly there were no There There were no significant differences in striatal metabolism in cocaine abusers tested suring late withdrawal.

The hypofrontality in the detoxified cocaine abusers was interpreted as a reflection of decreased DA activity into mesocortical projection since hypofrontality has been associated with conditions with decreased DA activity such as Parkinson's disease[47-51] and supranuclear palsy[52-56]. Furthermore the strong correlation observed in the cocaine abusers between frontal metabolism and D_2 receptor availability supports this hypothesis (bellow).

CORRELATIONAL STUDIES:

Because brain metabolism is tightly coupled with brain function, measurement of brain metabolism in addition to the various indices of DA activity allows the assessment of the functional changes associated with changes in brain DA activity. The following data summarizes the correlation analyses between DA D_2 receptor availability and regional brain glucose metabolism in the 20 cocaine abusers[41] and in four of the seven who had repeated scans 3 months after detoxification. The correlation analyses between DA D2 and metabolism revealed significant

correlations for several regions of the frontal cortex, most markedly orbito-frontal ($r = 0.70$ $p < 0.0001$), prefrontal ($r = 0.56$ $p < 0.005$) and cingulate cortices ($r = 0.63$ $p < 0.0005$) (figure 9).

Analyses of the correlation between ^{11}C-cocaine binding in the basal ganglia and regional glucose metabolism revealed a similar pattern of correlations to that seen with NMS with significant correlations limited predominantly to frontal cortex ($r=0.67$ $p<0.01$).

Because regional brain glucose metabolism primarily represents activity in the nerve terminal[57], this association could reflect activity from the ventral tegmental area since this region projects directly into the OFC, prefrontal, and cingulate cortices[58,59]. These cortical regions, in turn, could modulate striatal DA receptor availability via the cortico-striatal pathway[45] (Fig. 10A). The association could also reflect striatal modulation of frontal metabolism via the striato-pallidal-thalamic cortical pathway[60].

The mesolimbic DA system appears to be critical in mediating the reinforcing properties of cocaine and participating in its addiction liability[61,62]. Disruption of the mesocortical DA system from chronic cocaine use could lead to abnormal function in projection areas ie frontal cortical regions (orbitofrontal, cingulate and prefrontal regions, nucleus accumbens, hippocampus and amigdala[45] which could then give rise to the complex pattern of behaviours associated with addiction. In fact involvement of OFC, prefrontal and cingulate cortices in processes mediating positive reinforcement has been demonstrated in animal studies[63].

For example, one can distinguish an initial process by which the intake of the drug is experienced as pleasurable. This process of intrinsic reinforcing drug effects is the one associated with increased DA in nucleus accumbens and prefrontal cortex[21,64,61]. The memory of the drug experience and of the circumstances and the behaviors associated with the experience have also been shown to contribute to repeated cocaine intake[65]. With repeated administration, the ability of this memory to elicit a desire or "craving" for cocaine becomes more frequent and serves to perpetuate the use of cocaine[7]. The neurochemical and neuroanatomical substrates for consolidation of this memory and for eliciting cocaine craving are not well understood, but probably involve the hippocampus among other brain regions. While the memory and intrinsic reinforcing properties of cocaine are important, we hypothesize that other processes are also involved, since compulsive cocaine administration in the addicted individuals occurs despite rapid tolerance to the subjective effects of cocaine[66] and even in the presence of adverse physical reactions. The drive and loss of control leading to compulsive self-administration of cocaine is probably regulated both by DA and serotonin[67,68] and may involve orbito frontal, prefrontal and cingulate cortices. Other processes such as sensitization, have also been reported to occur with repeated cocaine administration[44] and may also participate in triggering and/or perpetuating compulsive drug self administration. Abnormalities in the amigdala could facilitate kindling and senaitization processes. Another contributor invoked in the facilitation of repeated cocaine use is the emotional reaction of the individual to the losses experienced from his/her cocaine addiction[7]. In particular, dysphoria during withdrawal has been associated with a higher relapse rate in the cocaine abuser[7]. One could postulate that because the mesolimbic DA system is involved with reward processes, its dysfunction in the cocaine abuser could intensify depressive symptoms such as anhedonia and loss of drive[69].

We postulate that DA abnormalities in the cocaine abuser lead to dysregulation of these frontal regions favoring the emergence of behaviors associated with addiction such as impulsivity, compulsion to self-administer cocaine[70], dysphoria and inability to restrain from using cocaine. Animal studies have documented a central role of frontal regions (orbito frontal, cingulate and prefrontal cortices) in reinforcing properties of drugs[63]. Abnormalities in other projection areas of the mesocortical DA system such as hippocampus and amigdala probably also contribute to the addictive behaviours. Because of the limited spatial resolution of the PET tomograph the function in these areas could not be evaluated.

STUDIES ON COCAINE PHARMACOKINETICS

The absolute uptake, regional distribution, and pharmacokinetics of cocaine in the human and baboon brain have been accomplished with PET and [11C]cocaine cocaine[37]. Studies of the pattern of distribution of C-ll cocaine in the human brain revealed an heterogeneous distribution with maximal uptake in basal ganglia. The uptake of [11C]cocaine in basal ganglia was reduced by preadministration of cocaine suggestying that it reflects specific binding. Computation of the striatal to cerebellar ratio (STR/CB) to normalize by a brain region which had no dopamine transporter revealed that cocaine preadministration decreased the ratio from 1.75 to 1.17 (figure 11).

Preadministration of nomifensine, a drug that binds to the dopamine transporter, alos decrease striatal upake of [11C]cocaine to the same extent as that observed when preadministering cocaine (figure 12). [11C]Cocaine striatal binding inhibition by nomifensine suggests that predominant binding of cocaine in striatum is to the dopamine transporter.

Pharmacokinetic studies of ll-C cocaine in human brain revealed a wide variability among individuals for cocaine uptake into the brain. Figure 13 shown the time activity curves for the uptake of [11C]cocaine in the first 8 normal volunteers investigated. Though the maximal uptake differed markedly among subjects the shape of the curve was remarkably similar. Cocaine's uptake into the brain was very fast and peaked activity was reached for most subjects between 4-8 min post injection (PI).

The clearence of cocaine from the brain was slower in the basal ganglia than in other subcortical regions, cortical areas or cerebellum (figure 14). Half peak clearnece of [11C]cocaine in basal ganglia was approximately 20 min PI and that in thalamus, cortex and cerebellum approximately 15 minutes (figure 14)..

The relevance of the unique pharmacokinetics oc cocaine, its fast uptake and clearence from monoamine transporters, is highlighted by the parallelism between the kinetics of uptake and clearance of cocaine in basal ganglia and the time-related changes in the intensity of the euphoria experienced after intravenous cocaine. In figure 15 we have averaged the time activity curves for uptake of [11C]cocaine in basal ganglia for the first 10 subjects and plotted it with the reported values of euphoria experienced after intravenous cocaine administration[70] (Figure 15).

SUMMARY AND CONCLUSION.

These studies document dopaminergic abnormalities in cocaine abusers. They also suggest a regulatory role of DA in frontal metabolism. The correlation of striatal D_2 receptor availability with metabolism was strongest for OFC, cingulate and prefrontal cortices. In cocaine abusers tested during early withdrawal (<1 week) the OFC was found to be hypermetabolic and metabolism in OFC and prefrontal cortices were found to be significantly associated with cocaine craving[32]. Thus, we postulate that repeated and intermittent DA stimulation, as seen during a cocaine binge, activates the prefrontal and OFC cortices increasing the drive to compulsively self-administer cocaine. During cocaine discontinuation and protracted withdrawal and with decreased DA stimulation, these frontal cortical regions become hypometabolic. Dopaminergic stimulation by a DA-enhancing drug and/or environmental conditioning will reactivate these frontal regions resetting the compulsion to self-administer cocaine and the inability to terminate this behavior.

The pharmacokionetic studies with [11C]cocaine are consistent with behavioral and pharmacological studies in animals as well as in vitro studies which have revealed that while the mechanisms for cocaine's reinforcing properties are complex, they partly involve the brain's dopamine system and also highlight the importance of cocaine's pharmacokinetic on its unique reinforcing roperties.

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ACKNOWLEDGMENT:

Research supported by NIDA RIDA06278, and DOE DE-ACO2-76CH00016.

FIGURE LEGENDS

Fig 1: Schematic diagram of the DA synapse illustrating the different tracers used to evaluate the various components of the DA system: 18Fn-methylspiroperidol (NMS) to measure D2 DA receptors, 11C cocaine to measure the DA transporters and FDG to measure regional brain glucose metabolism.

Fig 2. Ratio index in normal controls (n=10) and in cocaine abusers (n=7) scanned within one week of last cocaine use.

Fig 3. Ratio index in normal controls (n=20) and in cocaine abusers (n=20) scanned one to 7 weeks after last cocaine use.

Fig 4. Values for ratio index for cocaine abusers who were able to complete the 3 month detoxification. The values during the first evaluation were done 1-7 weeks after last cocaine use, those during the second evaluation were done 3 months later after completion of the inpatient rehabilitation program.

Fig 5 Correlation between DA receptor availability (Ratio Index) and the Beck Depression Inventory ($r=-0.70$ $p \leq 0.001$)

Fig 6. Regional brain glucose metabolism in 10 cocaine abusers tested within 1 week of cocaine use (early) and cocaine abusers tested 1-4 weeks after last use (late). Comparisons represent differences with metabolic values in normal controls ($p < 0.01$)

Fig 7. Regional brain glucose metabolism in prefrontal ( ) and obito frontal cortex (0) were correlated with the subjective sense for drug craving (1 = mild, 2 = moderate, 3 = severe).

Fig 8. Relative metabolic measures in a group of 20 normal controls and 20 cocaine abusers tested 1-7 weeks after detoxification (cocaine-1m). Seven of these patients were tested 3 months later(cocaine -3m). Significance represent differences from normal controls ($p < 0.01$). (L = left, R =right, F = frontal, P = parietal, T = temporal, OC = occipital, TH = thalamus, B = basal ganglia, CB = cerebellum.

Fig 9: Correlation between ratio index and brain glucose metabolism in orbito frontal cortex (circles) and in cingulate gyrus (triangles) expressed as umol/100gr/min.

Fig 10. Schematic diagrams of the mesocortical DA pathway with efferents from the Ventral Tegmental Area (VTA) into the frontal cortex and ventral stiatum and of the nigrostriatal pathway with efferents from the Substantia Nigra (SN) to the dorsal striatum. Interactions between frontal cortex and the striatum could occur via the cortico-striatal pathway (10A) or they could occur indirectly via the striato-pallidal-thalamo-cortical pathway (10B).

Fig 11. Effects of cocaine pretreatment in the striatum to cerebellar ratio for [11C]cocaine. Cocaine pretreatment (2mg/kg iv) significantly decreased the STR/CB ratio when compared with baseline (BSL).

Fig 12. Effects of nomifensine (NOM) on the stratum to cerebellar ratio (str/cb). Nomifensine decreased the ratio as compared with baseline (BSL).

Fig 13. Uptake of [11C]cocaine in basal ganglia in 8 normal volunteers. Notice the variability in peak uptake.

Fig 14. Time activity curve for [11C]cocaine in various brain regions (BG = basal ganglia, TH = thalamus, CTX = cortex, CB = cerebellum).

Fig 15 Time activity curves for the subjective experience of euphoria after intravenous cocaine and the uptake of [11C]cocaine in basal ganglia. Values for uptake of [11C]cocaine were rescaled so as to correspond with the scale for euphoria (0-1000). Notice the parallelism between both curves.