PET Study Reveals Brain Activation Differences

Cocaine addicts have an increase in activity after methylphenidate exposure, nonaddicts a decrease.

BY KERRI WACHTER
Senior Writer

PHILADELPHIA — The activation of certain regions of a drug addict's brain following drug use may shed light on the compulsive nature of addiction, according to data presented at the annual meeting of the Society of Nuclear Medicine.

Using ^{18}fluorodeoxyglucose PET imaging, researchers at Brookhaven National Laboratory in Upton, N.Y., found that cocaine addicts have an increase in brain activation in the orbitofrontal cortex after exposure to methylphenidate, which is similar in effect to cocaine. In contrast, healthy control subjects in the study had a decrease in activity in the same region, said Nora D. Volkow, M.D., lead researcher and director of the National Institute on Drug Abuse, Rockville, Md. "They're going in opposite directions. This becomes very significant."

The difference in the response to methylphenidate suggests that abnormal recruitment of the orbitofrontal cortex—which is involved with salience, attribution, motivation, and drive—may reinforce the saliency of the drug. Moreover, this region is associated with compulsive behaviors, "so its abnormal activation could underlie the compulsive drug intake that occurs in addicted subjects," Dr. Volkow said.

In the study, brain metabolism was measured in 21 cocaine-addicted men and 15 nonaddicted men as controls. All subjects underwent two PET scans. Both groups were imaged following two sequential placebos given 90 minutes apart and following two sequential doses of methylphenidate—0.5 mg/kg and 0.25 mg/kg—given intravenously 90 minutes apart.

The investigators used two sequential doses because cocaine abusers "do not take drugs in isolation—they do it compulsively," Dr. Volkow said. Methylphenidate was chosen because, like cocaine, it blocks dopamine transporters. In addition, cocaine users report that methylphenidate's effects are similar to those of cocaine.

Cocaine abusers were an average of 36 years old and met the DSM-IV criteria for cocaine dependence. They used 3 g of cocaine per week, with continuous use for at least 6 months prior to the study, and averaged 13 years of use.

In self-reports of feelings of being high, control subjects had a greater response to the first dose than the second dose. Cocaine abusers also reported a greater high with the first dose, but the magnitude of their response was much lower than for the control subjects, she said.

In self-reports of craving, the control subjects reported very little craving for methylphenidate. In contrast, the first methylphenidate dose induced very strong cravings in the cocaine users and the second (and lower) dose induced cravings that were not as strong.

When the researchers specifically compared the differences in brain metabolic response between placebo and methylphenidate, cocaine abusers had a significant increase in metabolism in the right orbitofrontal cortex, while normal subjects had a decrease in metabolism. For the cocaine abusers, this increased activity in the right orbitofrontal cortex corresponded well with self-reports of cocaine craving.

'Abnormal activation could underlie the compulsive drug intake that occurs' in addicts.

DR. VOLKOW

These findings lend credence to the hypothesis that the orbitofrontal cortex and anterior cingulate gyrus play a major role in the manifestation of drug addiction. "Both of these regions are extremely important in assigning saliency to stimulations and also in exerting inhibitory control," Dr. Volkow said.

In a related study, the researchers looked at the effect of expectation on brain activity in nonaddicted subjects.

Twelve healthy subjects with minimal prior drug experience (average age 33 years) were imaged using fluorodeoxyglucose PET under four conditions: the subject expected placebo and received placebo (baseline); the subject expected placebo but received methylphenidate; the subject expected methylphenidate and received methylphenidate; and the subject expected methylphenidate but received placebo. The order of the conditions was randomized for each patient. A dose of 0.5 mg methylphenidate was given intravenously 5 minutes prior to the PET scan.

Self-reports of high and drug effects from the subjects corresponded well with methylphenidate use, regardless of expectation. There was in increase in glucose metabolism, particularly in the cerebellum, when methylphenidate was given, regardless of whether or not it was expected. With the administration of unexpected methylphenidate, there were also increases in metabolism in the right frontal cortex. However, the expectation of methylphenidate alone activated the orbitofrontal cortex, which "is the same finding that we obtained in cocaine abusers," Dr. Volkow said.

The finding that there is no difference between expected and unexpected methylphenidate in nonabusing subjects contrasts studies with cocaine abusers, in which expectation enhanced the effect of methylphenidate. This bolsters the relevance of learned experiences on brain responses to drugs of abuse. Activation of the orbitofrontal cortex by expectation alone suggests this region is involved in the processing of unexpected stimuli, she said. ■

Naltrexone Therapy May Control Alcohol Abuse Over Long Term

BY MITCHEL L. ZOLER
Philadelphia Bureau

PARIS — Long-term therapy with naltrexone can help keep alcohol-dependent patients on the wagon, Barbara J. Mason, Ph.D., said in a poster presentation at the 24th Congress of the Collegium Internationale Neuro-Psychopharmacologicum.

In a controlled study, "patients randomized to naltrexone had a significantly longer latency to their first heavy drinking episode, and longer latency to dropout due to treatment failure," said Dr. Mason, director of the division of clinical pharmacology in the department of neuropharmacology at Scripps Research Institute in La Jolla, Calif.

"The results support using long-term treatment with naltrexone for alcohol-dependent patients who respond to [short-term] treatment with naltrexone," she explained.

Although alcoholism is often a chronic, recurrent syndrome, most clinical studies of drug treatments for alcoholism have only assessed acute efficacy. This study focused on naltrexone's long-term efficacy for preventing alcohol abuse.

The investigators began by enrolling 159 people with alcohol dependence to an open-label phase in which they received 50 mg naltrexone daily plus a weekly session of cognitive-behavioral therapy.

After 12 weeks, there were 92 responders, defined as those who had two or fewer heavy drinking days during the final 6 weeks of the short-term phase or at least a 50% reduction in their alcohol use during the same period. These 92 patients were then entered into the randomized, long-term phase of the study.

In the second phase, 48 people were randomized to continued treatment with 50 mg naltrexone daily for an additional 40 weeks. The other 44 participants went into the control group and were treated with placebo. At baseline, all patients in the randomized phase were consuming an average of 8.5 drinks per day and had consumed alcohol on an average of 69 of the 90 days preceding the start of naltrexone treatment.

The average age of all patients in the randomized phase was 47 years. About 70% were men, and about 70% were white.

During the long-term treatment period, 75% of the patients who remained on naltrexone treatment refrained from a return to heavy drinking, compared with 60% of those in the control group, a statistically significant difference.

The average time that patients remained in the long-term treatment phase of the study without treatment failure was 32 weeks for those who continued naltrexone treatment and 22 weeks for those who came off naltrexone, which also was a statistically significant difference.

The study was funded by the National Institute on Alcohol Abuse and Alcoholism, not by DuPont Pharmaceuticals Co., which is the marketer of naltrexone (Revia). ■

Social Workers Step Up Care for Substance Abuse

WASHINGTON — Social workers are providing care for individuals with substance use disorders at increasing rates, Mickey J.W. Smith said in a poster presentation at the annual meeting of the Association for Medical Education and Research in Substance Abuse.

The study data were collected by the National Association of Social Workers as part of a survey of 2,000 social workers funded in part by the Center for Substance Abuse Treatment, said Mr. Smith of the NASW.

The social workers reported that 27% of their clients in 2002 had a primary or secondary substance use disorder, up from 25% in 2000. Clients seen by social workers in organizational settings had higher rates of primary diagnoses, compared with those seen by social workers in private practice in 2000 and 2002 (9% vs. 6% both years). Clients seen in organizational settings also had higher rates of secondary diagnoses, compared with private practice in 2000 (20% vs. 13%) and 2002 (21% vs. 17%).

The total average number of hours social workers spent in addictions-specific training decreased slightly, from 4.4 hours in 2000 to 4.3 hours in 2002, Mr. Smith reported.

Overall, 65% of social workers took part in addictions-specific continuing education in 2002, compared with 68% in 2000. But participation in several other types of addictions-specific training increased: 39% of the social workers took formal coursework in 2002, up from 38% in 2000, and 26% engaged in clinical supervision activities in 2002, up from 24% in 2000. In addition, 18% of respondents took part in field placement in 2002, up from 16% in 2000, and 6% did volunteer work in 2002, compared with 5% in 2000.

—Heidi Splete