Target 'Cellular-Level' Activity in Dependence

BY RENÉE MATTHEWS

BETHESDA, MD. — Chemical dependence as a result of drug abuse occurs at the cellular level because of neurochemical dysregulation, and an evidence-based understanding of these chemical dynamics and of the circumstances that drive a person to abuse drugs could yield a more comprehensive and effective approach to treatment.

"Chemical dependence is a disease of the brain caused by genetic vulnerability as well as exposure to a drug, and possibly other environmental factors such as trauma and family influence," said Carlton Erickson, Ph.D., a researcher in addiction science at the University of Texas at Austin, at the annual conference of the Association for Medical Education and Research in Substance Abuse.

Specifically, dependence occurs because of a neurochemical dysregulation of the mesolimbic dopamine system (MDS), which also is called the medial forebrain bundle or the pleasure or reward pathway because of dopamine's association with mood regulation, motivation, and reward, he said.

"We assume that a certain genetic propensity together with drug use can lead to dysregulation of the MDS neurotransmitter processes, that is, when people use a particular drug , it 'connects to' or 'matches' the transmitter system that is not normal" and disrupts the cellular-level functioning of the pathway, Dr. Erickson said, adding that this connection occurs because drugs typically act on a single neurotransmitter system, and those systems are particularly vulnerable to the specific drugs.

Continued exposure of the MDS pathways to a drug leads to changes or adaptations in nerve function, which are known as neuroadaptations, and when these changes reach a threshold, it leads to compulsive drug use over which the individual has impaired control, he suggested.

'Chemical dependence should be treated by positively affecting the abnormal brain function—dysregulation—to reduce the need for the drug that is being abused.'

"The main symptom of chemical dependence is impaired control over the use of a drug, and the patient perceives this as a basic need for the drug," he emphasized.

The mesolimbic dopamine system is a grouping of axons that extends from the brain's amygdaloid region to the frontal, prefrontal, and anterior cingulate cortexes that regulate feelings of pleasure. The different regions of the brain along the route of the MDS are governed by certain neurotransmitters, for example, dopamine (pleasure) in the ventral tegmental area, amygdala, hippocampus, and nucleus accumbens; serotonin (cravings) in the hypothalamus; and gamma-aminobutyric acid (GABA; sleepiness), also in the nucleus accumbens. Some addictive drugs such as cocaine, LSD, or benzodiazepines match up with and target certain neurotransmitters (dopamine, serotonin, and GABA, respectively), which might explain why some people have a drug or drugs of choice. "Multiple dysregulation could explain a person's codependence on several drugs," Dr. Erickson suggested.

Other pairings between addictive drugs and neurotransmitters include heroin and endorphins, nicotine and acetylcholine, alcohol and glutamate and substance P, and marijuana and endocannabinoids.

If chemical dependence occurs at the cellular level, then it would make sense that the treatment should also work at the cellular level, Dr. Erickson said. "Drug abuse is seen as a problem that needs to be solved through education, coercion, punishment, environmental change, or maturation, whereas chemical dependence should be treated by positively affecting the abnormal brain function—dysregulation—to reduce the need for the drug that is being abused," Dr. Erickson said at the conference, which was also sponsored by Brown Medical School.

Abuse and dependence are serious conditions and both need to be addressed, but they are not the same, he added. Drug abuse is volitional (person has control over use), but chemical dependence is an involuntary brain disease, so each requires a different treatment strategy.

Among the current options for initiating recovery are the traditional 12-step programs, which encourage abstinence; counseling for behavioral modification; cognitive-behavioral therapy (CBT) and primary care management; and medical treatment, which could include the use of detoxification medications or medications that enhance abstinence (at the cellular level), such as reward blockers, and anticraving medications such as methadone, buprenorphine, and vaccines.

One could argue, Dr. Erickson said, that behavioral therapies probably also change brain chemistry. "In other words, [during behavioral therapy] the MDS dysregulation begins to move back toward normal. It cannot be totally normalized, just "pushed back" toward normal, in much the same way that medications change brain chemistry."

Although there are no direct brain imaging studies that show that this happens in dependence treatment, plenty of imaging research shows that psychotherapeutic methods such as CBT change brain function. Thus, "talk therapies" probably change brain function in a positive manner to help overcome dependence, said Dr. Erickson, who had no disclosures to make. ■

Cravings Complicate Withdrawal From Methamphetamine

BY BETSY BATES

LOS ANGELES — Persistent cravings, as opposed to a difficult struggle with withdrawal, are likely responsible for the grip of methamphetamine on addicted individuals who want to quit, according to results of an inpatient study presented at the annual meeting of the American Association of Addiction Psychiatrists.

Researchers at the University of California, Los Angeles, admitted 66 non–treatment-seeking methamphetamine-addicted patients and 89 healthy controls to an inpatient clinical research center for up to 5 weeks as part of several imaging studies conducted as those patients addicted to methamphetamine withdrew from the drug.

The addicted patients were active users at admission and were monitored daily via urine screening to ensure that they remained abstinent throughout their hospitalizations.

To study the "pure" effects of methamphetamine withdrawal, those addicted were excluded if they were simultaneously addicted to other substances (except nicotine) or if they had pre-existing psychiatric diagnoses or serious medical conditions, said Dr. Todd Zorick of the Center for Addictive Behaviors at UCLA.

Methamphetamine-dependent subjects were compared with matched healthy control subjects on the Beck Depression Inventory (mood), and Brief Symptom Inventory (general psychiatric symptoms, including hostility, anxiety, depression, and psychosis).

Addicted subjects experienced a variety of prominent withdrawal symptoms on days 1-3, including diarrhea, red/itchy eyes, suicidal thoughts, and mild psychotic symptoms.

Symptoms of psychoticism, obsessional behavior, interpersonal sensitivity, hostility, and paranoia, and somatic symptoms were "quite high" early on, particularly in the first 24-48 hours of abstinence.

On days 4-14, other symptoms came to the fore, including a lack of motivation, increased appetite, sleep difficulties, and fatigue, Dr. Zorick reported.

However, most of these symptoms were mild, manageable, and gradually declined over time.

"Pretty much anything we saw [in these symptom clusters] was gone in 2 weeks," he said.

Even after 5 weeks, patients in a controlled environment might be less depressed, sleeping better, and have fewer psychotic symptoms—but 'they are still thinking about meth a lot.'

Depression symptoms, which have been hypothesized to drive relapse, were elevated over those of healthy controls at study entry but generally declined over 4 weeks. Although a small subset of patients had Beck Depression Inventory scores that persisted at a mean level of about 12 on the 0-63 scale, most had scores at 1 month that were "at least as low or lower" than scores of healthy controls.

What did persist was craving, which began at a mean of 40-50 on a 0-100 visual analog scale and remained in the 20-30 range at the end of week 1.

Over the first 14 days of abstinence, cravings subsided somewhat, but for many users, the desire for methamphetamine did not completely wane even after a month had passed since last use.

"Even at week 5, [craving is] not zero," Dr. Zorick said. "These are people who haven't touched meth in 5 weeks. [They] are still thinking about meth a lot [in a controlled, hospital environment]…not being exposed to it whatsoever."

Craving scores were not associated with depression symptoms except during weeks 1 and 2 of abstinence, he noted.

Dr. Zorick said the results might serve to inform clinicians about the clinical course of withdrawal in their patients and the need to continue to address craving over the long term.

"If you get somebody in your office who recently quit methamphetamine or is trying to quit… he's likely to experience a lot of psychiatric symptoms, including hostility, paranoia, interpersonal sensitivity, and high levels of depression," he said. "These are not happy people.

"However, the good news is that these symptoms decrease to a pretty low baseline on average within the first 2 weeks or so."

At that time, "they are likely to feel a lot better, not experiencing depression, no psychotic symptoms, sleep normalized, but they may have high levels of craving for methamphetamine."

No drugs have been approved by the Food and Drug Administration to reduce craving in patients addicted to methamphetamine who are attempting to quit, although this should be a crucial goal for future research, Dr. Zorick said.

Dr. Zorick's research and that of Edythe London, Ph.D., also of UCLA and the principal investigator of the inpatient imaging studies, were sponsored by government grants.

Neither investigator reported any relevant financial disclosures. ■