Cocaine-induced brain plasticity may protect the addicted brain

27 August 2008

A new study has unraveled some of the mysteries of the cocaine-addicted brain and may pave the way for the design of more effective treatments for drug addiction. The research, published by Cell Press in the August 28 issue of the journal *Neuron*, identifies specific brain mechanisms that underlie addiction-related structural changes in the brain and provides surprising insight into how these changes may actually defend the brain during excessive drug use.

Persistence of drug-seeking behaviors after long periods of abstinence has presented a major challenge for treatment of addiction. It has been hypothesized that long-term physical changes in the brain might underlie enduring behaviors associated with drug abuse. One long-lasting structural correlate that has been observed across many models of addiction is an increase in the density of dendritic spines on medium-sized spiny neurons (MSNs) in the nucleus accumbens (NAc). The spines represent critical points of communication, called excitatory synapses, between brain cells. The density of these inputs could have a major impact on the way information is processed in the brain and may regulate addiction-related behaviors.

"Although several groups have documented that repeated cocaine exposure increases NAc spine density, the precise molecular mechanisms that control this process have remained elusive," says senior study author Dr. Christopher W. Cowan from the Department of Psychiatry at The University of Texas Southwestern Medical Center. "Moreover, the cocaine-induced increase in NAc spine density has been hypothesized to contribute to the long-lasting behavioral sensitization that occurs after repeated cocaine exposure, but direct evidence concerning the functional relationship between these two processes is lacking."

Previous work demonstrated that chronic cocaine exposure increased levels of cyclin-dependent kinase 5 (Cdk5) in the NAc and that inhibition of Cdk5 blocked the cocaine-induced increase in spine density. The myocyte enhancer factor 2 (MEF2) family of transcription factors are Cdk5 targets that are expressed throughout the developing and adult brain and have been implicated in the regulation of excitatory synapses.

Dr. Cowan and colleagues found that chronic cocaine exposure reduced MEF2-dependent transcription and promoted increased MSN dendritic spine density in the NAc. Unexpectedly, expression of an overactive form of MEF2 in the NAc that blocked cocaine-induced spine density was associated with an enhanced behavioral sensitivity to cocaine whereas reduction of endogenous MEF2 proteins reduced these behaviors. These results suggest that the cocaine-induced increases in dendritic spine density may actually limit behavioral changes associated with drug addiction rather than support them.

"Taken together, our findings implicate MEF2 as a key regulator of structural synapse plasticity and sensitized responses to cocaine and suggest that reducing MEF2 activity, and thereby increasing spine density, in the NAc may be a compensatory mechanism to limit long-lasting maladaptive behavioral responses to cocaine," concludes Dr. Cowan. "A better understanding of the MEF2-associated molecular mechanisms that regulate cocaine-induced structural and behavioral plasticity could ultimately lead to the development of improved treatments for drug addiction."

Source: Cell Press