small-scale projects that may provide a detailed look at the individual types of neurons. Sacha Nelson, MD, PhD, a professor of biology at Brandeis University in Waltham, Mass, is launching one such project, using gene expression and more traditional techniques to identify distinct neuron types.

During a presentation on November 14 at the annual meeting of the Society for Neuroscience in Washington, DC, Nelson described how he is using microarray technology to study gene expression in small groups of identified neurons. He explained that when microarray technology is used to analyze tissue from a particular region, the gene expression patterns of individual neuronal cell types might be lost. "When you chop out a chunk of mouse brain tissue, grind it up, and extract the RNA, things that might be altered in only one of these cell types are essentially impossible to see; they vanish into the noise," he said.

So he and his colleagues have begun identifying specific neuronal types, fluorescently labeling them, and then manually dissecting neurons of a specific neuronal cell type from a particular region. They then use microarray technology to analyze the gene expression of that neuronal cell type.

Nelson, who hopes to use this technique and others to begin better classifying the approximately 1000 neuronal types in the brain, said such projects will be key to better understanding many diseases of the brain.

"Most neurological diseases affect particular cell types," Nelson explained. For example, Huntington disease affects the medium spiny cell of the striatum, Alzheimer disease is a disorder of hippocampal pyramidal neurons and neocortical pyramidal neurons, and Parkinson disease results from degeneration of dopamine-producing neurons.

"In many cases, genes implicated in these diseases are present throughout the brain and in some cases throughout the body," Nelson said. "But there are important aspects of the cell biology and physiology of these neuronal cell types that contribute to these particular diseases."

To understand how these cell characteristics and genes interact, Nelson and his colleagues are developing mouse models in which they can manipulate the genes associated with neurological disease in specific types of neurons.

Nelson and scientists from both the Allen Brain Atlas project and GENSAT agree that using the new data sets and tools will lead to more animal experiments that involve the manipulation of genes in various neuronal cell types and brain regions. These experiments, in turn, may provide new insights into brain function and disease. □

Scientists Seek Cause of Drug Craving

Bridget M. Kuehn

FOR INDIVIDUALS BATTLING ADDICtion, memories of people, places, and other things they associate with using drugs can trigger powerful cravings. This phenomenon is considered one of the most pernicious aspects of addiction and has been studied as a potential target for treatment.

Animal models of addiction are beginning to provide clues to the molecular basis of this phenomenon and findings in recent years suggest glutamate receptors play an important role. Repeated administration of psychoactive drugs such as cocaine and amphetamine have been shown to cause craving-like behavior in mice and corresponding reduction in glutamate-mediated communication between cells in the nucleus accumbens, a part of the brain's reward system (Thomas MJ et al. *Nat Neurosci*. 2001;4:1217-1223).

Now, a new study by researchers from the University of British Columbia, in Vancouver, is providing further evidence that glutamate receptors and cell signaling in the nucleus accumbens play a role in drug craving. Using a rat model, Yu Tian Wang, PhD, Anthony G. Phillips, PhD, and colleagues found evidence suggesting that a reduced number of glutamate receptors in the nucleus accumbens caused by repeated drug exposure may account for drug-craving behavior. They also found a strategy that appears to reverse this process and stops craving behavior in rats (Brebner K et al. *Science*. 2005;310:1340-1343).

Phillips explained that repeated amphetamine administration causes cells in the nucleus accumbens to pull a particular type of glutamate receptor (the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA] receptor) into the cells' interior, leaving fewer AMPA receptors on the cell surface to communicate. In studies in cultured cells, the researchers foiled this process, using a biologically inert decoy peptide that resembles a portion of the tail of the AMPA receptor that is anchored inside the cell. The decoy tricks the cells into pulling these molecules inside, leaving the AMPA receptors on the cell's surface, allowing them to engage in glutamate-mediated communication with other cells. The decoy peptide can be fused to a virus protein that facilitates the passage of such proteins through the cell membrane and administered intravenously to rats exhibiting craving-like behaviors. This treatment extinguished the behaviors.

Later, the scientists used a tube inserted in the rats' brains to deliver the decoy peptide directly to either the nucleus accumbens or the ventral tegmental area and found that the craving-like behavior was extinguished only when the peptide was administered to the nucleus accumbens. This confirms the role of the nucleus accumbens.

The decoy peptide did not appear to have any adverse effects on the animals and did not appear to interfere

with memory or learning not associated with drug use, Phillips said. However, he noted, several steps remain before the team will feel confident that they have identified a potential treatment strategy, starting with verifying their findings in animal models of other aspects of addiction, such as relapse.

While much work remains, the study underscores that glutamate receptors may play an important role in addiction. Although many addiction studies have focused on the dopamine system in the brain, most researchers say that multiple brain systems are likely to be involved in this chronic, relapsing disease.

"The emerging story is dopamine and glutamate are both involved in important ways in the development of addiction," explained Phillips. "Dopamine undoubtedly is responsible for the emotional or the motivational effects of the drug and the glutamate system is probably what registers the memory of the drug experience." □