Two Nicotine Addiction Puzzles Explained

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The stranglehold of nicotine addiction leads to more than four million smoking-related deaths each year. Scientists at the California Institute of Technology have now explained two roots of that addiction. The discoveries may offer new hope not just for smokers, but eventually also for sufferers of Parkinson's disease, a debilitating movement disorder that affects some 40 million people worldwide.

Researchers have known for decades that chronic exposure to nicotine increases the number of nicotine receptors--molecules that are activated by binding to the drug--on nerve cells. The binding of nicotine to these receptors, and in particular to one specific subunit known as alpha4, enhances the release of a pleasure-causing neurotransmitter called dopamine.

But "this increase is confusing," says Henry A. Lester, the Bren Professor of Biology at Caltech, "because for opioid addiction, and for many other classes of addictions and of drugs in general, the body attempts homeostasis and adjusts the number of receptors downward if there is a constant stimulus." Understanding this paradox--how it is possible that smokers become tolerant to the pleasurable effects of nicotine despite the fact that their brains produce new nicotine receptors in response to the chemical--is crucial for defeating nicotine's addictive power.

Lester, his postdoctoral researcher Raad Nashmi, and their colleagues at Caltech, the University of Colorado at Boulder, and the University of Pennsylvania School of Medicine, have now solved the mystery, by

developing a special mouse strain with fluorescent nicotine receptors. These fluorescent tags allowed the scientists to monitor the effects of the nicotine throughout the brain, down to the level of individual neurons.

"We find that alpha4 containing receptors, those with some of the highest sensitivity to nicotine, are upregulated"--or increased in number--"by chronic nicotine in a cell-specific fashion," Lester explains. "In particular, the alpha4-containing receptors are indeed upregulated in the dopamine-producing portions of the brain, but not in the dopamine neurons themselves." Instead, the increase in receptor number occurs only in neurons that inhibit dopamine neurons--a group called the GABAergic neurons.

This surprising result led the researchers to conduct experiments with delicate electrical probes. In chronic nicotine-treated mice (and presumably in chronic smokers), the dopamine neurons are chronically inhibited from firing in the absence of nicotine. And nicotine itself still excites the dopamine neurons, leading to pleasure, but much less than expected.

"This research explains tolerance during nicotine addiction," Lester says. "Once in a while, an important piece of a puzzle does fall into place."

"This is outstanding work that will open the door to further studies of nicotinic receptor upregulation in the cognitive and rewarding effects of nicotine," comments Daniel S. McGehee of the University of Chicago, who studies the neurobiology of nicotine addiction. McGehee was not involved in the present research.

But there's more. In the special Caltech mice, the largest number of new nicotine receptors appeared in the mouse forebrain. This is the part of the brain involved in cognition. Electrical measurements showed that these new receptors also helped to boost synaptic transmission. The

result may explain why many smokers claim that cigarettes actually help them think better--and why 44 percent of the cigarettes smoked in the United States are consumed by people with mental health problems.

"People may attempt to medicate themselves with nicotine, and my research is also aimed at trying to understand the mechanism behind that," Lester says.

"We now think that we need to concentrate on drugs that manipulate upregulation." Lester adds. His lab is currently developing simpler cell-based systems using the fluorescently labeled nicotine receptors. Using special microscopes, the effect of particular drugs on those receptors can be monitored.

One long-term benefit of the research could be the development of better therapies for Parkinson's disease, the chronic neurological condition that gradually destroys some dopamine cells. Although the cause of Parkinson's disease is unknown in most patients, one curious observation is that few smokers are ever affected. In fact, they seem to be protected against the condition. The reason, researchers suspect, is nicotine--and the new brain studies reveal that the reason may be those cell-specific differences in the regulation of nicotine receptors.

Previously, animal models of Parkinson's have shown that the excessive activity of dopamine neurons, firing in hysterical bursts, can lead to the death of those neurons. The affected neurons are located in a brain region called the substantia nigra, which is a center of voluntary movement control.

"These dopamine cells are actually persuaded by chronic nicotine to fire less, which may help them to live longer," says Lester, who hopes the research will lead to the development of drugs that act "very specifically" on these nicotine receptors and prevent cell death, "so

people with the early stages of Parkinson's disease get the protection that they need."

The paper, "Chronic Nicotine Cell Specifically Upregulates Functional alpha4* Nicotinic Receptors: Basis for Both Tolerance in Midbrain and Enhanced Long-Term Potentiation in Perforant Path," was published in the August 1 issue of the *Journal of Neuroscience*.

Source: Caltech