# Dissecting the machinery of nicotine's reward

June 14 2006

Understanding what makes people crave the high of nicotine is a key to developing treatment for this highly addictive drug. And that understanding involves tracing the neural machinery by which nicotine switches on the brain's reward machinery.

In an article in the June 15, 2006, Neuron, Jean-Pierre Changeux of CNRS, Collège de France, and Institut Pasteur and Philippe Faure of Institut Pasteur and CNRS and colleagues revealed key details of how nicotine stimulates neurons that are an integral part of the reward circuitry. They also found that the same circuitry is involved in triggering exploratory and novelty-seeking behaviors. Their findings bring us a step closer to understanding regulation of that circuitry, information that is, as the researchers write, "crucial to understand the mechanisms responsible for the vulnerability to drugs of abuse."

In their experiments, the researchers sought to understand how nicotine stimulates particular receptors--called nicotinic acetylcholine receptors (nAChRs)--on the surface of neurons that produce the neurotransmitter dopamine. Such "dopaminergic" neurons are known to be central to turning on the brain's reward mechanism. The stimulation of nAChRs by nicotine makes them more responsive to their natural triggering neurotransmitter, acetylcholine (ACh).

Receptors such as nAChRs are complex proteins that nestle in the surface of cells and trigger cellular responses when activated by either a natural chemical or an external substance such as nicotine. Researchers studying the structure of nAChRs had found that they comprise many

components called subunits that influence the receptors' function. In particular, two subunits called ß2 and a7 had been implicated as important in nAChRs' response to nicotine.

Changeux and colleagues tested in mice how dopamine-producing neurons responded to nicotine when the researchers genetically removed either of these subunits. They found that dopaminergic neurons in mice lacking the ß2 subunit showed no response to nicotine compared to normal mice, in which nicotine enhanced the neurons' firing. However, mice lacking the a7 subunit did show a neuronal response to nicotine, although it was not the same response as in normal mice.

The researchers confirmed the importance of the ß2 subunit by using a harmless virus to reintroduce it back into the mice lacking it. They found that reintroduction in a specific region of the brain (the ventral tegmental area; VTA) was sufficient to restore the normal neuronal nicotine response. A prior study also showed that mice lacking the ß2 subunit also showed reduced exploratory behavior, which was also restored when the researchers added the subunit back. This finding thus showed that the dopaminergic brain circuitry was involved in such behaviors as curiosity or interest in novelty, wrote the researchers.

The researchers concluded that their "data suggest that a concomitant activation of [ß2 and a7 receptor subunits] may be a necessary requirement for the full expression of the sequence of events leading to nicotine reinforcement."

The researchers said that the findings "are consistent with the suggestion of a hierarchical role of the two subunits." While the ß2 subunit would mediate a "global tonic" regulation of dopamine-producing neurons by nicotine and acetylcholine, the a7 subunit would more finely tune the response of these neurons, they concluded.

Source: Cell Press