Reining in nicotine use: Midbrain habenula region plays key role in nicotine dependence

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A person's vulnerability to nicotine addiction appears to have a genetic basis, at least in part. A region in the midbrain called the habenula (from Latin: small reins) plays a key role in this process, as Dr. Inés Ibañez-Tallon and her team from the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, Germany, have now shown. They also shed light on the mechanism that underlies addiction to nicotine.

According to the World Health Organization WHO in Geneva, it is estimated that tobacco use kills more than five million people each year worldwide. Many of them die of lung cancer. "Two years ago, studies indicated that genetic variations in a specific gene cluster are risk factors for nicotine dependence and lung cancer," Dr. Ibañez-Tallon pointed out. She and her team, together with researchers from the Pasteur Institute in Paris, France and the Russian Academy of Sciences in Moscow, have now elucidated the mechanism underlying this dependence.

They investigated a specific receptor for the neurotransmitter acetylcholine, which is activated by nicotine in smokers and is encoded by this specific gene cluster, consisting of three subunits, that is three genes. "Although this gene cluster is present in the DNA of every cell, the receptor is only expressed in a few restricted areas of the brain. One of them is the habenula in the midbrain," Dr. Ibañez-Tallon explained.

The MDC researchers investigated this receptor and its subunits in egg cells of the African clawed frog (Xenopus laevis) and in transgenic mice. One of the three genes of the cluster is alpha5. "An important percentage of heavy smokers carry a single mutation in this gene. They are more prone to become addicted to nicotine and to develop lung cancer than individuals without this mutation," Dr. Ibañez-Tallon said.

Strong Aversion to Nicotine

A second gene in the gene cluster encoding this receptor is beta4. The MDC researchers demonstrated that transgenic mice expressing high levels of the beta4 gene have increased sensitivity to nicotine. These mice have a strong aversion to drinking water containing nicotine.

However, when the researchers expressed the mutated variant of the alpha5 gene via a lentivirus in the habenular brain region of these mice, after only two weeks the mice showed a preference for nicotine. Dr. Ibañez-Tallon and her colleagues conclude that only a balanced activity of these two genes can rein in nicotine use.

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