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Habenular Tcf7l2 links nicotine addiction to diabetes

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The neuropeptide glucagon-like peptide-1 (GLP-1) was shown recently to enhance sensitivity of medial habenula (mHb) neurons to nicotine and thereby exert inhibitory control over nicotine intake. Little is known about the intracellular mechanisms through which GLP-1 acts. Here, we tested the hypothesis that the transcription factor Tcf7l2, considered a core component of the GLP-1 signaling cascade, regulates the actions of nicotine on mHb neurons to control nicotine intake. We found that Tcf7l2 is highly enriched in mHb and, using a new line of *Tcf7l2* mutant rats, that Tcf7l2 deficiency increases nicotine self-administration behavior. CRISPR-mediated cleavage of *Tcf7l2* in the mHb similarly increased nicotine self-administration in mice. Using whole-cell electrophysiological recordings and RNA sequencing, we found that Tcf7l2 regulates the recovery of nicotinic acetylcholine receptors in the mHb from nicotine-induced desensitization through a mechanism involving local cAMP signaling. Notably, both *TCF7L2* mutations and a history of tobacco smoking increase the risk of type-2 diabetes through unknown mechanisms. We found that doses of nicotine that activate the mHb increased blood glucose levels in rodents and that Tcf7l2 knockdown in mHb blocked this effect. Moreover, repeated exposure to hyperglycemic doses of nicotine elevated circulating levels insulin and glucagon and induced diabetes-like disruption of blood glucose homeostasis. *Tcf7l2*^{mut} rats were resistant to nicotine-induced perturbations in blood glucose homeostasis. Together, these findings demonstrate that Tcf7l2 regulates the stimulatory effects of nicotine on mHb neurons to control nicotine intake and hyperglycemic responses to the drug, potentially explaining the link between *TCF7L2* mutations diabetes and tobacco smoking.