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HOT TOPICS

Habenular TCF7L2 links nicotine addiction to diabetes: the broad significance

Stephanie P. B. Caligiuri[1] and Paul J. Kenny[1]

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Tobacco smoking is a leading cause of disease and premature death. Even in nonsmokers the tobacco habit can be deadly, with over 880,000 people worldwide estimated to die each year from diseases related to secondhand smoke exposure [1]. As might be expected, the tobacco habit is associated with diseases of the respiratory system, including lung cancer, chronic obstructive pulmonary disease (COPD), and asthma. Tobacco smoking also contributes to non-respiratory system diseases. Notably, the risk of type 2 diabetes (T2D) is much higher in current than former or never smokers. How tobacco smoking contributes to T2D has been unclear but was thought to reflect actions of nicotine at nicotinic acetylcholine receptors (nAChRs) in the pancreas. The medial habenula (mHb) contains some of the highest densities of nAChRs in the brain and is known to regulate aversive reactions to nicotine that promote avoidance of the drug [2]. The mHb also densely expresses the diabetes-associated transcription factor transcription factor 7 like 2 (TCF7L2) [3], which is a core component of the signaling cascade associated with glucagon-like peptide-1 (GLP-1). GLP-1 is an incretin hormone that acts on the pancreas to enhance insulin secretion. GLP-1 also acts on mHb neurons to promote nicotine avoidance [4]. Recently, our laboratory established that doses of nicotine that activate the mHb markedly elevate blood glucose levels in male and female rodents [3]. CRISPR-mediated genomic cleavage of *Tcf7l2* in the mHb abolishes the hyperglycemic actions of nicotine and dramatically increases nicotine intake [3]. The stimulatory effects of nicotine on the mHb are greatly attenuated in genetically modified rats that express a truncated form of TCF7L2 that cannot be activated by GLP-1 [3], which reflects deficits in TCF7L2-mediated recovery of nAChRs from nicotine-induced desensitization. Chronic nicotine treatment disrupts blood glucose homeostasis in wild-type rats, reflected by elevated fasting blood glucose and glucagon levels, and TCF7L2 mutant rats are resistant to this action of nicotine [3]. Virus-tracing experiments identified a polysynaptic connection from mHb to the pancreas, via the autonomic nervous system (ANS), providing a mechanism by which the mHb can influence blood glucose homeostasis [3]. These findings suggest that nicotine elevates blood glucose and confers risk of T2D through TCF7L2-dependent actions on the mHb. More broadly, these findings suggest that TCF7L2 regulates a habenula–pancreas axis that links the addictive-relevant behavioral actions of nicotine to its diabetes-promoting actions. That nicotine in cigarettes, vaping devices or transdermal patches can act on the habenula to modulate ANS control of pancreas, and likely other organ systems, has important implications for our understanding of the etiology of tobacco-related diseases. For example, T2D and other diseases associated with ANS dysfunction in smokers and nonsmokers could reflect abnormalities in brain–body interactions [5]. If so, novel therapeutics designed to modulate brain–body communication could be used to treat T2D and other smoking-related diseases. By extension, currently available diabetes therapeutics could potentially exert some of their beneficial effects through actions in the brain [6]. Another important consideration is whether organ systems and physiological processes outside the brain that are impacted by nicotine, such as maintenance of blood glucose levels, can in turn modulate the function of brain circuits involved in reward and motivation. If so, peripheral organs may play a previously unrecognized role in the etiology of tobacco dependence and other substance use disorders. Ultimately, as our understanding of brain–body interactions increases, it may be necessary to broaden brain-centric conceptualizations of drug addiction to encompass the notion of "whole-body" perturbations.

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AUTHOR CONTRIBUTIONS

SPBC and PJK wrote the paper.

ADDITIONAL INFORMATION

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REFERENCES

1. Oberg M, Jaakkola MS, Woodward A, Peruga A, Pruss-Ustun A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. Lancet. 2011;377:139–46.
2. Fowler CD, Lu Q, Johnson PM, Marks MJ, Kenny PJ. Habenular alpha5 nicotinic receptor subunit signalling controls nicotine intake. Nature. 2011;471:597–601.
3. Duncan A, Heyer MP, Ishikawa M, Caligiuri SPB, Liu XA, Chen Z, et al. Habenular TCF7L2 links nicotine addiction to diabetes. Nature. 2019;574:372–77.
4. Tuesta LM, Chen Z, Duncan A, Fowler CD, Ishikawa M, Lee BR, et al. GLP-1 acts on habenular avoidance circuits to control nicotine intake. Nat Neurosci. 2017;20:708–16.

[1]Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
Correspondence: Paul J. Kenny (paul.kenny@mssm.edu)

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5. Schwartz MW, Seeley RJ, Tschop MH, Woods SC, Morton GJ, Myers MG, et al. Cooperation between brain and islet in glucose homeostasis and diabetes. Nature. 2013;503:59–66.

6. Ryan KK, Li B, Grayson BE, Matter EK, Woods SC, Seeley RJ. A role for central nervous system PPAR-gamma in the regulation of energy balance. Nat Med. 2011;17:623–6.