

Smokeless Weight Loss

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Smoking and obesity are two leading causes of chronic disease in the developed world. Given that the combined impact of these factors on health can be especially deleterious, it is somewhat ironic that smoking is known to have beneficial effects on body weight; smoking is one of the easiest and most reliable approaches to weight loss, at least for low-level smokers (≤ 10 cigarettes/day) (1). This phenomenon provides the opportunity to target—and possibly tap into—the mechanisms underlying nicotine's actions on weight loss. We know, for example, that nicotine stimulates hypothalamic acetylcholine receptors, eventually activating anorexigenic arcuate proopiomelanocortin neurons; melanocortin-4 receptors appear to be crucial to these actions (2). This is particularly interesting because genetic variants affecting the melanocortin system, especially melanocortin-4 receptors, are among the most well-described genetic contributors to human obesity (3,4). The question remains as to how nicotine's actions on this brain system ultimately affect appetite and metabolism. This is where we pick up the story: extending the mechanisms of nicotine's actions on weight loss to effectors including brown adipose tissue (BAT) and locomotor activity.

In recent years, BAT has become a hot area of study (so to speak) as a result of the discovery of BAT-like tissues and actions in humans (5). The old dogma that there was no BAT in adult humans has now been put to rest. This has prompted a flurry of studies probing how BAT thermogenesis is controlled, how it may account for differential obesity propensity, and how it might be used to combat weight gain. The ventromedial hypothalamus (VMH) is one of several hypothalamic, midbrain, and hindbrain energy balance nuclei that are key components of the hypothalamic-BAT axis (6). In this issue of *Diabetes*, Martínez de Morentin et al. (7) demonstrate that hypothalamic nicotine impacts the core molecular mechanism that integrates information controlling energy balance: AMP-activated protein kinase (AMPK). They showed that nicotine dephosphorylates and inactivates AMPK and affects its targets (including acetyl-CoA carboxylase and fatty acid synthase) in the VMH. The importance of hypothalamic AMPK in the control of food intake (8) suggests that this action of nicotine likely underlies its ability to suppress appetite. Martínez de Morentin et al. propose that changes in energy expenditure also result from nicotine-induced activation of hypothalamic AMPK and that nicotine alters AMPK activity in the

VMH to enhance BAT thermogenesis, thereby completing the circuit. Moreover, they demonstrate that nicotine withdrawal, which is known to negate nicotine-induced weight loss (9,10), rapidly reverses nicotine's effects both in the hypothalamus and in BAT; the low respiratory quotient (indicating the use of fat as fuel) and heightened locomotor activity also abate. The data further support a role for brain AMPK mediating nicotine's actions. Much of nicotine's effects on appetite and energy expenditure are nullified or reduced by activating AMPK with either AICAR or viral vector-mediated constitutively active AMPK. Activating AMPK with AICAR significantly blunts the ability of nicotine to decrease appetite and adiposity and reverses nicotine's suppressive effect on the orexigenic neuropeptides neuropeptide Y and agouti-related protein. In essence, these data suggest that nicotine taps into the brain's core sensing and integration mechanisms, controlling both energy intake and energy expenditure.

The work by Martínez de Morentin et al. reflects emerging trends in energy balance investigation directed at understanding how hormones, neurotransmitters, and other agents induce coordinated changes in energy balance through alterations in both energy intake and expenditure via both behavioral and physiological outputs. Their results also raise several interesting questions. How much impact does nicotine-induced energy expenditure, particularly BAT thermogenesis, contribute to overall energy balance compared with its potent suppression of appetite? Although it is clear that nicotine induces BAT thermogenesis, other aspects of energy expenditure are also affected, such as locomotor activity. Indeed, there is evidence to support the idea that smoking heightens whole-body energy expenditure in people through activity-related energy expenditure, including decreased activity economy (11,12). Other questions raised by these findings include how nicotine's actions in hypothalamic AMPK ultimately alter locomotor activity and the associated energy expenditure, and how much this contributes to energy balance and weight loss. We know that overlapping regions of the hypothalamus can regulate skeletal muscle fuel use through a circuit similar to that which ultimately activates BAT (13–16). The idea that brain activation of sympathetic outflow mediates nicotine's effects on peripheral metabolism is also supported by data from smokers (17). Continuing work in smokers and animal models will determine how all of these actions might contribute to fuel utilization (18,19), metabolic flexibility, glucose tolerance, cardiovascular disease, and resistance to diabetes.

In an effort to answer some these intriguing questions, we can refer back to studies on smoking and smoking cessation. The ability of smoking to increase energy expenditure is dampened in high-level smokers compared with low-level smokers (1); smoking leads to long-lasting tolerance to the metabolic effects of nicotine (1,9), and smoking cessation results in a rebound in body weight and metabolism (10). The findings described by Martínez de Morentin et al. are consistent with results from human

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studies not only in the peripheral means through which nicotine affects metabolism but also in relation to the ability of nicotine to rapidly alter brain substrates controlling both arms of energy balance. A complete picture is emerging with respect to how smoking alters core features of energy balance homeostasis. As we move forward, there will be additional aspects to consider, including the influence of culture and social environment, cognition, and reward, all of which interact to affect both energy balance and nicotine use (20). Emerging work is focusing on how these factors affect appetite, metabolism, and smoking. This will surely result in a more complex, but also more comprehensive, picture of smoking and weight control.

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