Published in final edited form as:
Cell Metab. 2011 August 3; 14(2): 145–147. doi:10.1016/j.cmet.2011.07.006.

The Smoking Gun in Nicotine-Induced Anorexia

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Abstract

Hypothalamic proopiomelanocortin (POMC) neurons are the major source of anorectic melanocortin peptides in the brain. A recent study (Mineur et al., 2011) demonstrates that nicotine directly stimulates arcuate POMC neurons through nicotinic acetylcholinergic α3β4 receptors, suggesting a new mechanism to understand the inverse relationship between tobacco smoking and body weight.

It has been widely noted that people increase their food intake and gain weight after quitting smoking (Williamson et al., 1991). This change in feeding behavior has been considered to be due to increased anxiety resulting from self-restraint against the desire of lighting a cigarette. Both nicotine and food have powerful reinforcing properties, which make tobacco smoking and excessive caloric intake among the major increasing medical burdens in most modern societies. Although nicotine and the consumption of palatable food independently increase dopamine release in the nucleus accumbens, nicotine decreases food intake and cigarette smokers generally weigh less and are leaner than nonsmokers. A recent report published in *Science* by Mineur and colleagues (Mineur et al., 2011) elaborates a new perspective to explain the inverse relationship between smoking and eating. Through a combination of molecular, pharmacological and behavioral approaches, the authors provide evidence demonstrating that nicotine diminishes food intake by stimulating receptors that are located on POMC neurons, which play a fundamental role in modulating satiety.

A decade ago it was shown that the adipostatic hormone leptin is able to increase the activity of a group of neurons present in the arcuate nucleus of the hypothalamus that express the proopiomelanocortin gene (*Pomc*) (Cowley et al., 2001). POMC encodes a prohormone that gives rise to α-, β-, and γ-melanocortins that act as potent satiety signals upon stimulation of melanocortin receptors located in the paraventricular nucleus of the hypothalamus (Cone, 2005). Thus, leptin, mainly produced in adipose tissue, acts as a peripheral hormone that enters into the brain carrying the ability to control food intake in part by stimulating leptin receptors expressed on hypothalamic POMC neurons that promote anorexia. The neurotransmitter serotonin (5-HT) is also able to activate arcuate POMC neurons via stimulation of 5-HT_{2C} receptors (Heisler et al., 2002), a discovery that helped to explain the anorectic effects of D-fenfluramine and other previously prescribed amphetamine-like

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molecules. POMC neurons also receive inhibitory signals from nearby neurons expressing neuropeptide Y (NPY) and GABA, which in turn are stimulated or inhibited by the gut peptides ghrelin and PYY_{3-36}, respectively (Batterham et al., 2002; Cowley et al., 2001). Thus, nicotine can now be added to a growing list of hormones, peptides and neurotransmitters that regulate the activity of POMC neurons and ultimately the release of anorectic melanocortins (Fig. 1).

Mineur and colleagues showed in their study that prolonged treatment with nicotine, or the α3β4 agonist cytisine, decreased food intake in mice (Mineur et al., 2011). Mecamylamine, a nicotinic antagonist that crosses the blood-brain barrier blocked these effects, while hexamethonium that is excluded from the brain was ineffective, indicating that nicotine's anorectic action occurs in the central nervous system. Confirmation that the anorectic effects of nicotine involved central cholinergic receptors harboring β4 subunits was provided by an elegant experiment performed with an adeno-associated virus (AAV) expressing short hairpin inhibitory RNA targeted specifically to β4 mRNA and stereotactically delivered to the ventral hypothalamus. The β4 knockdown mice were insensitive to the anorectic effects of cytisine, however, they did not show hyperphagia per se suggesting a low basal cholinergic tone on POMC neurons.

The authors then showed that α3β4 ACh receptors are localized within the somatodendritic portion of POMC neurons. Although laser capture microdissection of POMC-GFP neurons followed by RT-PCR can sometimes amplify false positive mRNAs from contaminating nearby cells, the electrophysiological data provided definitive proof that nicotine and cytisine are able to depolarize membrane potential and strongly increase action potential frequency of POMC-GFP neurons. The authors showed that the nicotinic receptor antagonist mecamylamine had no effect on the spontaneous activity of POMC neurons but surprisingly, they did not use this drug to block the depolarizing effects of nicotine or cytisine or report the percentage of POMC neurons studied that were excited by the agonists. In an effort to demonstrate in vivo that nicotine-induced satiety involved activation of POMC neurons and release of melanocortin peptides, the authors showed that POMC knockout mice were insensitive to the anorectic effects of nicotine or cytisine, as were mice with AAV-mediated short hairpin inhibitory RNA knockdown of melanocortin 4 receptors in the paraventricular nucleus of the hypothalamus.

Although the work by Mineur et al. represent an interesting start, further studies are still needed to determine if ACh plays a physiological role in the regulation of POMC neurons and the control of food intake. It will be of interest to define the anatomical origin of cholinergic fibers releasing ACh in the arcuate nucleus and to determine the functional significance of the endogenous stimulation of the α3β4 receptors present on POMC neurons. All the effects shown in this paper were found after the pharmacological application of nicotine or the α3β4 agonist cytisine. Since the prolonged administration of the central nicotinic antagonist mecamylamine produced no effect on food intake, it is unlikely that a central cholinergic pathway plays a major tonic effect in feeding behavior. Finally, although the authors studied the effect of nicotine and cytisine to elicit excitatory postsynaptic potentials (EPSCs) on POMC neurons, applying trains of depolarizing stimulations through a second electrode in the vicinity of the recording electrode will be important to detect electrically evoked EPSCs that could be prevented by nicotinic receptor blockers.

Whether or not endogenous ACh significantly modulates the activity of POMC neurons, the results of Mineur and colleagues put forward the idea that selective α3β4 drugs may act as novel appetite suppressants and/or prevent excessive food intake in people quitting cigarette smoking. This approach is analogous to the use of varenicline (Mihalak et al., 2006), a nicotinic partial agonist based on the structure of cytisine, that has been approved by the

U.S. Food and Drug Administration for use as a smoking cessation aid. Although varenicline is more potent on α4β2 and more efficacious on α7, respectively, than on α3β4 nicotinic receptors, development of novel selective compounds for this latter receptor subtype could potentially act as a safe stimulator of POMC neurons to aid reduced food intake without causing the negative side effects observed with some nicotinic drugs such as cardiovascular stimulation and psychomotor depression.

Acknowledgments

Work in the authors' laboratories is supported in part by National Institutes of Health grant DK068400 (MJL and MR).

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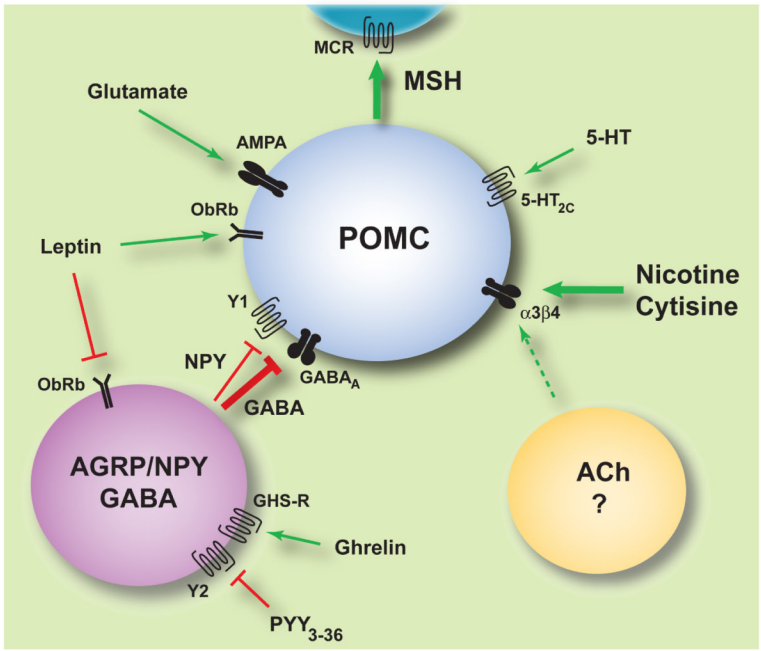

Figure 1. Arcuate POMC neurons integrate a diverse set of excitatory and inhibitory signals involved in the central regulation of energy balance

Hormones, peptides, and neurotransmitters modulate the membrane potential and action potential frequency of POMC neurons through their actions on excitatory (green) and inhibitory (red) receptor-signal transduction mechanisms. These effects are both direct and indirect, as emphasized by the interaction of AGRP/NPY/GABA neurons and POMC neurons. The balance of excitatory and inhibitory inputs ultimately controls the release of melanocortin peptides, which act through melanocortin receptors (MCR) to inhibit food intake. New data demonstrate a direct excitatory action of nicotine and the α3β4 nicotinic acetylcholinergic receptor-selective agonist cytisine on POMC neurons. However, the source and magnitude of endogenous ACh innervation of arcuate POMC neurons remain unknown.