Nicotine, Food Intake, and Activation of POMC Neurons

The effect of smoking on appetite is well known to smokers. Individuals who quit smoking gain on average 11–15 pounds in the first 2 years of abstinence, and adolescent girls, in particular, may smoke to control their weight (Stice and Shaw, 2003). As we know well from warnings of public health organizations, there is also a growing obesity epidemic in the United States and across the developed world. Unfortunately, the increase in obesity comes at a time that smoking has declined somewhat, and the New England Journal of Medicine has suggested that the increase in obesity is likely to offset any gains in life expectancy from decreases in smoking (Stewart *et al*, 2009). Thus, understanding the mechanisms through which smoking decreases appetite could be important in developing novel treatments for individuals who resist quitting for the fear of gaining weight.

Nicotine is likely to be the component in cigarette smoke that decreases appetite (Grunberg *et al*, 1987). Using a combination of pharmacological, molecular genetic, electrophysiological and feeding studies, we have identified the molecular and cellular mechanisms underlying nicotine's ability to decrease food intake (Mineur *et al*, 2011). In brain slices through the arcuate nucleus of the hypothalamus from mice expressing green fluorescent protein under control of the pro-opiomelanocortin (POMC) promoter, we found that nicotine increases the firing rate of POMC neurons, a critical component of a circuit mediating satiety. Although nicotine can increase the firing of both POMC and neuropeptide Y-expressing neurons in the arcuate nucleus (Huang *et al*, 2011), expression of POMC and subsequent activation of melanocortin 4 (MC4) receptors in the paraventricular nucleus (PVN) of the hypothalamus are critical for nicotinic-induced

decreases in appetite. Both knockout of the *POMC* gene or knockdown of MC4 via viral-mediated delivery of small hairpin RNAs to the PVN greatly decreased the effect of nicotine on food intake in mice (Mineur *et al*, 2011). Importantly, the nicotinic acetylcholine receptors (nAChRs) that mediate the effect of nicotine on food intake contain the $\beta 4$ subunit, which distinguishes these nAChRs from those involved in the rewarding and reinforcing properties of nicotine that lead to addiction containing the $\beta 2$ subunit (Picciotto *et al*, 1998). This is of interest as novel therapeutics targeting the nAChRs involved in food intake would therefore not be likely to show addiction liability.

nAChRs are normally stimulated by the neurotransmitter acetylcholine that is released from cholinergic neurons in several brain areas. The identification of nicotinic control of POMC neuron activity and its role in the appetite suppressing effects of nicotine pinpoints a mechanism that was previously unknown for acetylcholine receptors for to regulate appetite; however, the source of acetylcholine innervating neurons in the hypothalamus and the conditions leading to acetylcholine release are not known. These studies therefore suggest that acetylcholine release in the arcuate nucleus can normally alter the activity of POMC neurons and could, in turn, affect energy expenditure and feeding patterns. Targeting these nAChRs could be important in developing novel smoking cessation aids that also prevent weight gain.

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DISCLOSURE

The authors declare no conflict of interest.

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PACAP and the PAC1 Receptor in Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) affects approximately 5–10% of all individuals and is more predominant in women (Breslau, 2001). Advances in treatment and prevention will require identifying biomarkers to aid early diagnosis and understanding the mechanisms underlying maladaptive responses to trauma.

In a highly traumatized, urban civilian population, we have recently reported that women (but not men) that had been diagnosed with PTSD had higher blood PACAP (pituitary adenylate cyclase-activating polypeptide) levels (Ressler *et al*, 2011) (Figure 1a). The high PACAP levels were correlated with physiological measures of the acoustic startle reflex, which have previously also been associated with PTSD risk. In addition, to further understand the responsiveness of the PACAP system to emotionally relevant cues and ovarian hormones, we showed that mRNA levels of the receptor for PACAP–PAC1R, are increased in the extended