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 β4 subunit, which distinguishes these nAChRs from those involved in the rewarding and reinforcing properties of nicotine that lead to addiction containing the β2 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.

ACKNOWLEDGEMENTS

This work was supported by NIH grant DA014241.

Marina R Picciotto[1] and Yann S Mineur[1]
[1]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
E-mail: marina.picciotto@yale.edu

DISCLOSURE
The authors declare no conflict of interest.

Grunberg NE, Winders SE, Popp KA (1987). Sex differences in nicotine's effects on consummatory behavior and body weight in rats. *Psychopharmacology (Berl)* **91**: 221–225.

Huang H, Xu Y, van den Pol A (2011). Nicotine excites hypothalamic arcuate anorexigenic proopiomelanocortin neurons and orexigenic neuropeptide Y neurons: similarities and differences. *J Neurophysiol* **106**: 1191–1202.

Mineur YS, Abizaid A, Rao Y, Salas R, DiLeone RJ, Gundisch D *et al* (2011). Nicotine decreases food intake through activation of POMC neurons. *Science* **332**: 1330–1332.

Picciotto MR, Zoli M, Rimondini R, Léna C, Marubio LM, Merlo Pich E *et al* (1998). Acetylcholine receptors containing the beta-2 subunit are involved in the reinforcing properties of nicotine. *Nature* **391**: 173–177.

Stewart ST, Cutler DM, Rosen AB (2009). Forecasting the effects of obesity and smoking on U.S. life expectancy. *New England J Med* **361**: 2252–2260.

Stice E, Shaw H (2003). Prospective relations of body image, eating, and affective disturbances to smoking onset in adolescent girls: how Virginia slims. *J Consult Clin Psychol* **71**: 129–135.

Neuropsychopharmacology Reviews (2013) **38,** 245; doi:10.1038/npp.2012.163

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

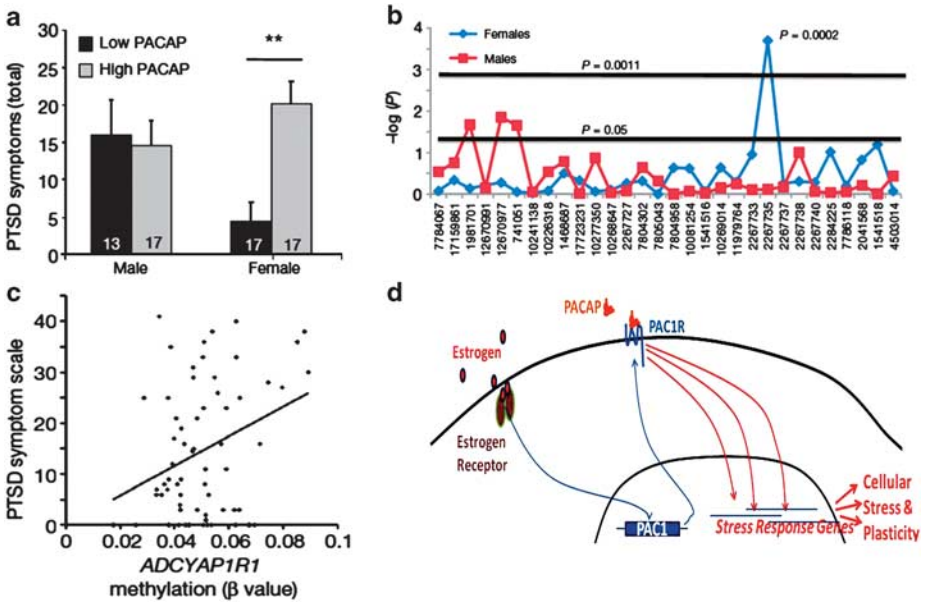

Figure 1. Relationship between the pituitary adenylate cyclase-activating polypeptide (PACAP)–PAC1 receptor (PAC1R) system and post-traumatic stress disorder (PTSD). (a) Females, but not males with high plasma PACAP38 levels show more PTSD symptoms. (b) rs2267735 is the only SNP spanning the PAC1R gene that is significantly associated with PTSD symptoms in females, not males. (c) Epigenetic modifications are observed at the PAC1R gene with PTSD symptoms being positively correlated with methylation at the PAC1R locus. (d) Working hypothesis to suggest that the responsiveness of the PACAP and PAC1R system to estrogen might be important in the sex-bias in PTSD prevalence. (a, b, and c reproduced from Ressler *et al*, *Nature* (2011)).

amygdala of adult rodents following classical fear conditioning and as a function of estrogen exposure. These findings suggested that PACAP might be involved in the symptoms characteristic of women diagnosed with PTSD.

To further genetically probe this association, we analyzed the PACAP (Adcyap1) gene and its receptor-PAC1 (Adcyap1r1). Only the Adcyap1r1 SNP (rs2267735) was found to be associated with PTSD diagnosis in women (again not in males) (Figure 1b). Although note that this SNP association was not replicated in a less traumatized cohort (Chang *et al*, 2012). At the epigenetic level, we also found that differential methylation of the Adcyap1r1 gene was associated with PTSD symptoms (Figure 1c). Given the approximately 2 : 1 sex-bias in PTSD prevalence, we find it exciting that the Adcyap1r1 SNP is within a predicted estrogen response element (ERE). Furthermore, in a postmortem sample, we found that females had differential cortical expression of Adcyap1r1 mRNA levels as a function of their genotype. Notably, a recent follow-up study finds that the same genetic risk is associated with higher acoustic startle in traumatized boys and girls before puberty, suggesting that the estrogen effect may be age-dependent (Jovanovic *et al*, 2012).

Looking to the future, the association between PTSD and the PACAP–PAC1 receptor system in traumatized populations warrants further investigation on several important levels. For example, longitudinal prospective studies are needed to ascertain whether peripheral PACAP levels would serve as a robust predictive biomarker of eventual PTSD diagnosis. The PACAP–PAC1 receptor system has been studied for its role in stress responsiveness (Vaudry *et al*, 2009; Stroth *et al*, 2011), and as such presents a convergence between the stress and learning components of PTSD that should be investigated further. The genetic observation of a predicted ERE supports other findings that hormonal mechanisms may underlie the sex-bias in PTSD prevalence (Ferree *et al*, 2011; Lebron-Milad and Milad, 2012), but replications of this finding are necessary. Finally, learning is accompanied by epigenetic modifications at key genetic loci (Zovkic and Sweatt, 2012), and probing the epigenetic signatures at the Adcyap1 and Adcyap1r1 genes as a result of previous traumatic experience or hormonal condition presents fertile ground for empirical analysis (Figure 1).

In summary, the relationship between PTSD and the PACAP–PAC1 receptor system affords us the opportunity to address PTSD from the perspectives of stress physiology, endocrinology, epigenetics, and predictive biomarkers using human samples and animal modelsFa truly multipronged attack that may be required for understanding complex neuropsychiatric disorders.

Brian G Dias[1] and Kerry J Ressler[1]

[1]HHMI and Emory University Department of Psychiatry and Behavioral Sciences, Yerkes Research Center, Atlanta, GA, USA

E-mail: kressle@emory.edu

DISCLOSURE

The authors declare no conflict of interest.

Breslau N (2001). The epidemiology of posttraumatic stress disorder: what is the extent of the problem? *J Clin Psychiatry* **62**(Suppl 17): 16–22.

Chang SC, Xie P, Anton RF, De Vivo I, Farrer LA, Kranzler HR *et al* (2012). No association between ADCYAP1R1 and post-traumatic stress disorder in two independent samples. *Mol Psychiatry* **17**: 239–241.

Ferree NK, Kamat R, Cahill L (2011). Influences of menstrual cycle position and sex hormone levels on spontaneous intrusive recollections following emotional stimuli. *Conscious Cogn* **20**: 1154–1162.

Jovanovic T, Norrholm SD, Davis J, Mercer KB, Almli L, Nelson A *et al* (2012). PAC1 receptor (ADCYAP1R1) genotype is associated with dark-enhanced startle in children. *Mol Psychiatry* doi:10.1038/mp.2012.98 (Epub ahead of print).

Lebron-Milad K, Milad MR (2012). Sex differences, gonadal hormones and the fear extinction network: implications for anxiety disorders. *Biol Mood Anxiety Disord* **2**: 3.

Ressler KJ, Mercer KB, Bradley B, Jovanovic T, Mahan A, Kerley K *et al* (2011). Posttraumatic stress disorder is associated with PACAP and the PAC1 receptor. *Nature* **470**: 492–497.

Stroth N, Holighaus Y, Ait-Ali D, Eiden LE (2011). PACAP: a master regulator of neuroendocrine stress circuits and the cellular stress response. *Ann NY Acad Sci* **1220**: 49–59.

Vaudry D, Falluel-Morel A, Bourgault S, Basille M, Burel D, Wurtz O *et al* (2009). Pituitary adenylate cyclase-activating polypeptide and its receptors: 20 years after the discovery. *Pharmacol Rev* **61**: 283–357.

Zovkic IB, Sweatt JD (2012). Epigenetic mechanisms in learned fear: implications for PTSD. *Neuropsychopharmacology* **38**: 77–93.

Neuropsychopharmacology Reviews (2013) **38,** 245–247; doi:10.1038/npp.2012.147

Psychosis is Emerging as a Learning and Memory Disorder

The difficulty in developing mechanistic models for psychiatric diseases may be that we are using the incorrect disease targets. Recently, clinical scientists have been attempting to examine alterations in dimensions of cognition and affect, rather than diagnoses of neuropsychiatric disease for clues to neural mechanisms of psychopathology. The RDoCs (Research Domain Criteria) (http://www.nimh.nih.gov/research-funding/rdoc/nimh-research-domain-criteria-rdoc.shtml) system is a leading example of this reorientation. In RDoCs, dimensions of cognition and affect (alterations of which combine to compose the psychiatric diseases that we know) are the unifying, homogenous units generating psychopathology. 'Psychosis' is a ready example and can be conceptualized as a learning and memory disorder. We have been studying this dimension across psychotic diagnoses, with the goal of identifying the normal cognition system(s) whose pathology could generate psychosis (Ivleva *et al*, 2012).

The hippocampus is altered in schizophrenic psychosis, with structural, functional, and molecular pathology; specifically, psychosis is associated with increases in basal hippocampal activity and reductions in associational memory processing (Tamminga *et al*, 2010). The hippocampus is one of the most actively studied regions in brain; initial studies were focused on human memory, stimulated by HM, and more recent research has greatly extended early studies to explicate systems of signaling molecules involved in memory computations, as well as changes in synaptic plasticity underlying learning and memory. Hippocampal structures, including subfields, fiber pathways, and the one-way trisynaptic circuit, are critical in generating normal memory behaviors; subfields contribute uniquely to memory. Memory behaviors emerge from the smooth functioning and proper connectivity of dentate gyrus and the cornu ammonis fields of CA3 and CA1 (Liu *et al*, 2012). Neural activity in the mossy fiber pathway from DG to CA3 can cause categorical changes in CA3 activity, dependent on the level of afferent stimulation from DG (Pelkey and, McBain, 2008). And within CA3, the recurrent collateral system is dependent on a controlled positive feed-forward system for productive 'pattern completion' function (Kremin and Hasselmo, 2007). Molecular and anatomic synaptic markers of memory-associated plasticity are well described (Abraham and Bear, 1996). These protein markers of normal memory behavior can be examined in human tissue to test for psychosis risk factors that could underlie psychosis.

It is plausible that psychosis is dependent on a pathologically increased level of neuronal function in CA3, which exceeds the associational capacity of this subfield and results in mistaken and false associations, some with psychotic content, which then get consolidated, as normal memory, albeit with psychotic content. These memories utilize normal declarative memory neural pathways, including limbic and prefrontal cortical regions, even though they have psychotic content. To demonstrate these ideas will require convergent sources of evidence from humans with psychosis using multimodal brain imaging, behavioral testing, and human tissue chemistry to create confidence in this kind of a novel approach. Our recent findings, including increased molecular plasticity-related proteins in CA3 accompanied by increased perfusion in CA3 and CA1 measured by MR, show the power of convergent methodologies. Finding the common elements in hippocampal pathology across the psychotic disorders would support new dimensional disease concepts.

Carol A Tamminga[1]

[1]Department of Psychiatry, UT Southwestern Medical School, Dallas, TX, USA

E-mail: Carol.Tamminga@utsouthwestern.edu

DISCLOSURE

The author is a Science Council Member in NAMI Scientific Council, Brain & Behavior Research Foundation (formerly NARSAD) and NIMH Board of Scientific Counselors; on the Editorial Board of American Journal of Psychiatry; an organizer at the International Congress on Schizophrenia Research; *ad hoc* consultant for Intra-Cellular Therapies, Astellas Pharma US, PureTech Ventures, Eli Lilly and Sunovion; has received Kempf Award from American Psychiatric Association; and is the Scientific Advisor to Lieber Institute for Brain Development/John Hopkins, Baltimore.

Abraham WC, Bear MF (1996). Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci* **19**: 126–130.

Ivleva EI, Shohamy D, Mihalakos P, Morris DW, Carmody T, Tamminga CA (2012). Memory generalization is selectively altered in the psychosis dimension. *Schizophr Res* **138**: 74–80.

Kremin T, Hasselmo ME (2007). Cholinergic suppression of glutamatergic synaptic transmission in hippocampal region CA3 exhibits laminar selectivity: Implication for hippocampal network dynamics. *Neuroscience* **149**: 760–767.

Liu X, Ramirez S, Pang PT, Puryear CB, Govindarajan A, Deisseroth K (2012). Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature* **484**: 381–385.

Pelkey KA, McBain CJ (2008). Target-cell-dependent plasticity within the mossy fibre-CA3 circuit reveals compartmentalized regulation of presynaptic function at divergent release sites. *J Physiol* **586**: 1495–1502.

Tamminga CA, Stan AD, Wagner AD (2010). The hippocampal formation in schizophrenia. *Am J Psychiatry* **167**: 1178–1193.

Neuropsychopharmacology Reviews (2013) **38,** 247; doi:10.1038/npp.2012.187