Mayans, Aztecs, and indigenous Americans cultivated tobacco for medicinal and religious purposes well over 2,000 years ago. The subsequent trade and industrial-scale production of tobacco have led to its global recreational use with devastating health consequences. It is currently responsible for the greatest number of preventable deaths worldwide by any single agent, estimated to be 5 million per year by the Center for Disease Control and Prevention. The active ingredient of tobacco, nicotine, efficiently permeates the blood brain barrier and activates neuronal nicotinic acetylcholine receptors (nAChRs) in the brain. In addition, nicotine exposure of the brain during childhood and adolescence is likely to increase susceptibility to neuropsychiatric and addiction disorders.

A multitude of distinct nAChR subtypes is formed by the assembly of α1–α7, α9, and β1–β4 subunits in mammals. These nAChR subtypes are expressed in different populations of neurons and other types of cells. The nAChRs most relevant to the study of nicotine addiction are expressed in dopaminergic, glutamatergic, and GABAergic neurons, where they modulate the probability of neurotransmitter release at presynaptic terminals (Wonnacott, 1997). Studies in rodents show that nicotine use affects various behaviors (Russo et al., 2010), including (a) impulse control and attention by modulating prefrontal cortex functions, (b) reward salience by modulating the ventral tegmental area (VTA)-striatum functions, and (c) aversive salience by modulating the medial habenula-interpeduncular nucleus functions.

Multiple nAChR subtypes mediate nicotine’s actions in the brain at the nanomolar concentrations found in smokers’ serum. The α4β2 nAChRs in VTA projections to the nucleus accumbens (Picciotto et al., 1998; Tapper et al., 2004), the α6α4β2β3 and α6β2β3 in substantia nigra pars compacta projections to the striatum (Quik et al., 2011), and the α3α5β4 and/or α4α5β2 in medial habenula projections to the interpeduncular nucleus (Fowler et al., 2011) collectively mediate nicotine’s complex behavioral effects. These nAChRs exhibit different channel kinetics, rates of desensitization, and affinities for the endogenous neurotransmitter, acetylcholine, and nicotine.

Nicotine exposure, unlike exposure to most other drugs of abuse, results in the “up-regulation” of its cognate nAChRs mediated by an increase in their abundance at the cell surface membrane in human, rodent, and primate brains (Schwartz and Kellar, 1983; Breese et al., 1997; Marks et al., 1998; Mamede et al., 2007; Nashmi et al., 2007). Both the α4β2 nAChRs (Kuryatov et al., 2005; Sallette et al., 2005; Lester et al., 2009) and the α6* nAChRs (Walsh et al., 2008; Henderson et al., 2014) are up-regulated when nAChR-expressing cells are exposed to nanomolar nicotine concentrations as found in smokers’ brains. In rodent brains, up-regulation appears to be a posttranscriptional effect: mRNA for neither the α4 nor the β2 nAChR subunits change after chronic nicotine exposure. The mechanism(s) by which nicotine up-regulates the α4β2 nAChRs, in particular, has attracted substantial attention because of the profound effect nAChR up-regulation has on the functional circuitry in which these nAChRs are expressed.

Based on experiments primarily done in vitro, which to a large degree mimic the up-regulation observed in vivo, many different mechanisms for up-regulation have been proposed (Govind et al., 2009). These include (a) decreased nAChR turnover at the plasma membrane, (b) increased nAChR affinity for nicotine itself caused by an induced conformational change in the receptor, (c) increased trafficking of nAChR to the plasma membrane, and (d) chemical chaperoning by nicotine to catalyze subunit assembly in the ER. Among the various mechanisms proposed, a preponderance of evidence supports the intracellular chemical chaperoning effects of nicotine.

In this issue, Henderson et al. showed that nicotine up-regulates α6* nAChRs in dopaminergic, medial habenula, and superior colliculus neurons of a knock-in mouse expressing a GFP-labeled α6 nAChR subunit. They then used normalized Förster resonance energy transfer (FRET) between the fluorescent labeled α6 nAChR subunit and intracellular transport vesicle and organelle proteins to study mechanistic aspects of nicotine-dependent up-regulation of recombinant α6β2β3 nAChRs expressed in vitro in Neuro-2a cells. By following FRET signals between the α6 nAChR subunit and proteins at the ER exit site, in coat protein complex I (COPII)- and COPI-coated vesicles, and the cis-Golgi, they found something quite unexpected about the ability of nicotine to up-regulate α6β2β3 nAChRs. Blocking the

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Nicotine alters its receptor’s ER–Golgi dynamics

Edward N. Pugh Jr. served as editor.

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Published December 30, 2013