Drug and Alcohol Dependence 141 (2014) 107–117

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Scientific overview: 2013 BBC plenary symposium on tobacco addiction

M. De Biasi[a,b,c,*], I. McLaughlin[a,b], E.E. Perez[c], P.A. Crooks[d], L.P. Dwoskin[e], M.T. Bardo[f], P.R. Pentel[g], D. Hatsukami[h]

[a] Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[b] Department of Neuroscience, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[c] Department of Neuroscience, Baylor College of Medicine, Houston, TX, USA
[d] Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR, USA
[e] Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, KY, USA
[f] Department of Psychology, University of Kentucky, Lexington, KY, USA
[g] Department of Medicine, Hennepin County Medical Center, University of Minnesota, Minneapolis, MN, USA
[h] Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA

ARTICLE INFO

Article history:
Received 6 February 2014
Received in revised form 12 May 2014
Accepted 16 May 2014
Available online 2 June 2014

Keywords:
Nicotine withdrawal
Nicotinic receptor antagonists
Nicotine dependence
Smoking cessation
Nicotine vaccine
Tobacco product regulation

ABSTRACT

Nicotine dependence plays a critical role in addiction to tobacco products, and thus contributes to a variety of devastating tobacco-related diseases (SGR 2014). Annual costs associated with smoking in the US are estimated to be between $289 and $333 billion. Effective interventions for nicotine dependence, especially in smokers, are a critical barrier to the eradication of tobacco-related diseases. This overview highlights research presented at the Plenary Symposium of Behavior, Biology and Chemistry: Translational Research in Addiction Conference (BBC), hosted by the UT Health Science Center San Antonio, on March 9–10, 2013. The Plenary Symposium focused on tobacco addiction, and covered topics ranging from basic science to national policy. As in previous years, the meeting brought together globally-renowned scientists, graduate student recruits, and young scientists from underrepresented populations in Texas and other states with the goal of fostering interest in drug addiction research in young generations.

1. Introduction

Nicotine, the alkaloid primarily responsible for the addictive properties of tobacco products, acts at nicotinic acetylcholine receptors (nAChRs). Found throughout the nervous system, nAChRs comprise numerous combinations of α (α2–9) and β (β2–4) subunits in the form of homo- and heteromeric ion channels (Gotti et al., 2009). nAChRs can mediate either fast synaptic transmission – as they primarily do in the periphery – or modulate the function of other neurotransmitter systems, as is common in the central nervous system (Dani and Bertrand, 2007; De Biasi, 2002).

The majority of smokers desire to quit, but only a small fraction of attempts are ultimately successful (Benowitz, 2010). According to the Center for Disease Control (CDC), approximately 69% of smokers want to quit, and 52% of smokers attempted to quit in 2010—but only 6.2% were successful (Centers for Disease Control and Prevention, 2011).

There are several issues to confront when considering smoking cessation. First, nicotine's ability to interfere with the dopaminergic (DA) reward system is an important factor contributing to both the initiation and maintenance of nicotine use (Picciotto and Corrigall, 2002). Second, smoking is also motivated by the urge to alleviate affective, cognitive, and physical symptoms of withdrawal that emerge during periods of abstinence (De Biasi and Dani, 2011). Although driven by the pharmacological effects of nicotine, addiction to tobacco is influenced by non-pharmacological factors, including cue and context associations, and stress. Those non-pharmacological elements play a major role in cue reactivity, evoked craving, and relapse to smoking (Bedi et al., 2011; Ray et al., 2013; Wray et al., 2013). Therefore, to be successful, smoking cessation strategies must reduce both the motivation to smoke, the symptoms of withdrawal during quit attempts, and craving. Nicotine replacement therapy (NRT), bupropion, and varenicline are the most commonly applied pharmacological aids for smoking cessation. Although all three work better than placebo, long-term success rates remain low among smokers attempting

* Corresponding author at: Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA.
Tel.: +1 12158989579.
E-mail address: marielde@mail.med.upenn.edu (M. De Biasi).

http://dx.doi.org/10.1016/j.drugalcdep.2014.05.013
0376-8716/

to quit (Paolini and De Biasi, 2011). The following summarizes progress that contributing authors' labs are making toward understanding the molecular mechanisms of nicotine addiction, as well as the design of pharmacological and non-pharmacological strategies aimed at improving smoking cessation outcomes.

2. Nicotinic receptor subunits and their influence on nicotine addiction and withdrawal

2.1. Symptoms of nicotine withdrawal

Several pre-clinical behavioral tests are available to explore the circuit- and cell-based mechanisms underlying nicotine withdrawal symptoms. The unpleasant symptoms associated with nicotine withdrawal act as negative reinforcers that promote nicotine dependence (Koob and Volkow, 2010; Piper et al., 2011; Allen et al., 2008). These negative reinforcers include both affective (anxiety, depression, and irritability) and somatic (decreased heart rate, constipation, general restlessness) symptoms (Malin and Goyarzu, 2009; Salas et al., 2009). Mice chronically exposed to nicotine display withdrawal symptoms that develop spontaneously, peak 24 h following cessation of administration, and can last for several days. Withdrawal can also be precipitated by systemic injection of non-selective nAChR antagonists such as mecamylamine (Paolini and De Biasi, 2011). Affective signs of withdrawal can be examined in rodents using behavioral paradigms that test for anhedonia, conditioned place aversion, anxiety, and conditioned fear (De Biasi and Salas, 2008; Damaj et al., 2003; Epping-Jordan et al., 1998; Davis et al., 2005). Physical signs of withdrawal include chewing, teeth-chattering, shakes, tremors, writhing, palpebral ptosis, gasps, and yawns (De Biasi and Salas, 2008; Malin and Goyarzu, 2009).

2.2. A gene cluster on chromosome 15q25 influences nicotine addiction

Ample studies have demonstrated that genetic factors predispose individuals to younger smoking initiation, increased quantities of cigarettes smoked, nicotine dependence, and smoking persistence (Li et al., 2003; Rhee et al., 2003; Schnoll et al., 2007). A cluster of nicotinic receptor genes (*CHRNA5*/*CHRNA3*/*CHRNB4*) located on chromosome 15q25 has been repeatedly associated with nicotine dependence, smoking behaviors, and lung cancer (Amos et al., 2008; Berrettini et al., 2008; Furberg et al., 2010; Greenbaum and Lerer, 2009; Hung et al., 2008; Liu et al., 2010; Rose, 2007; Saccone et al., 2010, 2007; Thorgeirsson et al., 2008). SNPSs rs16969968, rs578776, and rs588765 represent three statistically distinct nicotine dependence loci associated with the CHRNA5/A3/B4 gene cluster (Saccone et al., 2009, 2010). The α5 risk variant, rs16969968 G/A, causes an Asp398Asn amino acid substitution, and the risk allele (Asn398) produces hypofunctional α5-containing nAChRs with reduced Ca^{2+} permeability and faster desensitization rates than non-risk alleles (Bierut et al., 2008; Kuryatov et al., 2011). Other polymorphisms are associated with different levels of α5 or α3 mRNA (Wang et al., 2009), and the functional significance of several other gene variants in the CHRNA5/A3/B4 gene cluster is currently being investigated (Flora et al., 2013).

2.3. nAChR mutant mice help reveal mechanisms of nicotine withdrawal symptoms

Pre-clinical rodent models can be used to elucidate the functions of genes and brain pathways involved in nicotine addiction. The De Biasi lab took advantage of genetically engineered mice carrying null mutations in nAChR subunit genes to examine the roles of various subunits in the mechanisms of withdrawal. We focused on physical symptoms of nicotine withdrawal—studied either 24 h after nicotine deprivation, or upon systemic injection of mecamylamine in mice given free access to nicotine in drinking water. We found that mice lacking functional β4 nAChR subunits exhibited reduced somatic signs relative to wild-type mice undergoing nicotine withdrawal (Salas et al., 2004). Further experiments with additional mice lacking nAChR subunits revealed that physical symptoms of withdrawal also depend on α5, α2, and partially on α7 nAChR subunits (Salas et al., 2007, 2009). Interestingly, mice lacking the β2 nAChR subunit displayed symptoms of withdrawal resembling those of wild-type mice (Fig. 1). Mice carrying a null mutation for the α3 nAChR subunit were not studied due to perinatal mortality (Xu et al., 1999).

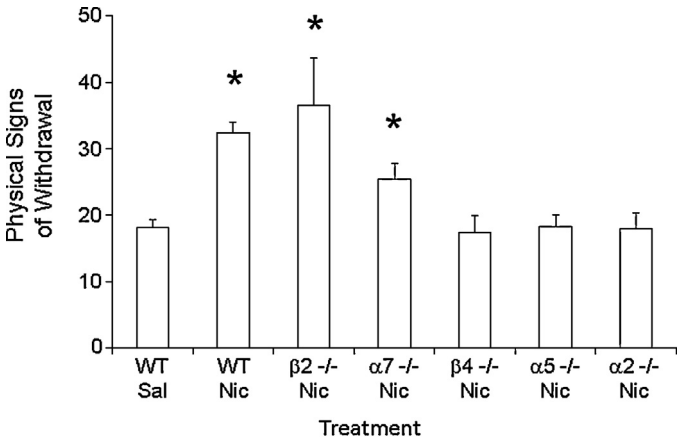

Fig. 1. *Lack of β4, α5 or α2 nAChR subunits protects against increases in nicotine withdrawal-induced somatic signs.* Various nAChR null mice and their wild type littermates were treated chronically with nicotine (24 mg/kg/day free base) or saline, using a mini-osmotic pump, for two weeks. On day 14, each mouse received a 3 mg/kg injection of the nonselective nicotinic antagonist, mecamylamine. Somatic signs were measured for 20 min. Mecamylamine treatment precipitated increases in somatic signs in wild type, β2 null, and α7 null mice chronically treated with nicotine. Such increases were not observed in β4, α5, or α2 null mice—suggesting that nAChRs containing these subunits participate in the modulation of nicotine withdrawal symptoms. * $p < 0.05$. The numbers within the bars indicate the number of animals tested for each strain. (Modified and adapted from Salas et al., 2004, 2007, 2009).

2.4. Medial habenula (MHb) and interpeduncular nucleus (IPN) are key brain areas for physical manifestations of nicotine withdrawal

We focused on the MHb–IPN pathway – which is among the brain areas with the highest co-expression of α5, α3, α2, and β4 – to pursue neuronal circuits associated with physical symptoms of withdrawal (De Biasi and Dani, 2011). The MHb, together with the lateral habenula (LHb), forms the habenular complex (Hb). The IPN is the main projection target of the MHb, while the LHb sends projections to the rostromedial tengmental nucleus (RMTg) in the midbrain. These brain areas play significant roles in aversion, negative reinforcement, negative prediction errors, and negative motivation (De Biasi and Dani, 2011; Fowler and Kenny, 2014). In mice chronically treated with nicotine, mecamylamine administration was sufficient to induce nicotine withdrawal behaviors only when microinjected into the MHb or the IPN, but not when microinjected into other brain areas, including the ventral tegmental area (VTA; Salas et al., 2009).

2.5. Future studies

One unanswered question is whether the MHb–IPN pathway and the nAChRs contained therein, are important for the affective manifestations of nicotine withdrawal. This is a key question, given