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Review

# Whole tobacco smoke extracts to model tobacco dependence in animals

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ABSTRACT

Smoking tobacco is highly addictive and a leading preventable cause of death. The main addictive constituent is nicotine; consequently it has been administered to laboratory animals to model tobacco dependence. Despite extensive use, this model might not best reflect the powerful nature of tobacco dependence because nicotine is a weak reinforcer, the pharmacology of smoke is complex and non-pharmacological factors have a critical role. These limitations have led researchers to expose animals to smoke via the inhalative route, or to administer aqueous smoke extracts to produce more representative models. The aim was to review the findings from molecular/behavioural studies comparing the effects of nicotine to tobacco/smoke extracts to determine whether the extracts produce a distinct model. Indeed, nicotine and tobacco extracts yielded differential effects, supporting the initiative to use extracts as a complement to nicotine. Of the behavioural tests, intravenous self-administration experiments most clearly revealed behavioural differences between nicotine and extracts. Thus, future applications for use of this behavioural model were proposed that could offer new insights into tobacco dependence.


**Contents**



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## 1. Role of nicotine in tobacco dependence

Smoking tobacco is globally the single most preventable cause of death. During 2011, tobacco use killed almost 6 million people worldwide and, if current trends continue, approximately 1 billion smokers are projected to die during the twenty-first century (Eriksen et al., 2012). Tobacco contains thousands of chemicals (Rodgman and Perfetti, 2013; Stedman, 1968), many of which are known carcinogens. As a result, chronic obstructive pulmonary disease, cardiovascular disease, chronic bronchitis, emphysema, strokes and many forms of cancer are directly attributable to smoking (Eriksen et al., 2012; Forey et al., 2011; Glantz and Gonzalez, 2012; Kuklina et al., 2012; Schwartz et al., 2007). The most insidious aspect of smoking is that it is highly addictive. More than half of smokers attempt to quit each year but only a small proportion are successful in maintaining long-term abstinence (Borland et al., 2012; Okuyemi et al., 2000; Rigotti, 2002). Furthermore, relapse can still occur a year or more following initial smoking cessation (Hawkins et al., 2010; Kerr et al., 2011; Piasecki, 2006). Consequently there is an urgent need to better understand and work towards reducing tobacco dependence.

It is well established that the main addictive constituent in tobacco is nicotine (Benowitz, 1988, 2009; Dani and Balfour, 2011). Nicotine is a naturally occurring alkaloid in tobacco and is present in all tobacco products at varying levels. It acts as an agonist at the acetylcholine nicotinic receptors (nAChRs) that are widely distributed throughout the brain. The nAChRs comprise a number of ligand-gated ion channel pentameric receptors, which are usually composed of two $\alpha$ and three $\beta$ subunits to form a pore (Laviolette and van der Kooy, 2004). Twelve neuronal nAChR subunits have been identified: $\alpha_2$–$\alpha_{10}$ and $\beta_2$–$\beta_4$ (Dani and De Biasi, 2001; Laviolette and van der Kooy, 2004), where the most abundant nAChRs in the brain are $\alpha_4\beta_2$ and the $\alpha_7$ receptors, the latter comprising only $\alpha_7$ subunits (Lena and Changeux, 1997; Lukas et al., 1999).

The $\alpha_4\beta_2$ receptors are the primary binding sites for nicotine and have a role in the development of tobacco dependence (Brennan et al., 2010; Buisson and Bertrand, 2001; Dani and Heinemann, 1996; Picciotto et al., 1998). Typically chronic agonist exposure leads to a downregulation of receptors (Creese and Sibley, 1981; Overstreet and Yamamura, 1979), yet paradoxically, chronic tobacco exposure produces functional $\alpha_4\beta_2$ receptor upregulation (Wonnacott, 1990; Vallejo et al., 2005).

The nAChRs have extensive neuromodulatory ability. For example, these receptors have been localised to glutamatergic (Jones and Wonnacott, 2004; Mansvelder and McGehee, 2000), dopaminergic (Marubio et al., 2003), serotonergic and $\gamma$-aminobutyric acid (GABA) (Yin and French, 2000) axon terminals across numerous brain regions. Consequently, nicotine can modulate acetylcholine (ACh) (Nordberg et al., 1989), dopamine (DA) (Liu et al., 2006; Sziraki et al., 1999), serotonin (5-HT), norephinepherine (NE) (Rossi et al., 2005; Sershen et al., 2009), glutamate (Liu et al., 2006) and GABA (Zhu and Chiappinelli, 1999) neurotransmission.

Despite these widespread effects, nicotine's impact on the mesocorticolimbic DA pathways has been most studied with respect to addiction (Clarke and Pert, 1985; Clarke et al., 1985; Wada et al., 1989). Activation of these pathways with concomitant elevations in extracellular DA levels in regions such as the nucleus accumbens (NAc), have been strongly associated with drug-produced reinforcement (Corrigall et al., 1992; Di Chiara, 2000; Di Chiara and Imperato, 1988; Phillips et al., 2003). Specifically, nicotine binds to nAChRs in the ventral tegmental area (VTA) (Laviolette and van der Kooy, 2003; Nisell et al., 1994b), which is followed by enhanced DA overflow in the NAc (Di Chiara, 2000; Nisell et al., 1994a).

The serotonergic system also seems to contribute to the addictive properties of smoking. Brain 5-HT systems have a prominent role in the regulation of mood and anxiety. Since nicotine alters serotonergic neurotransmission, these nicotine-produced changes might be associated with its antidepressant-like properties (Salin-Pascual et al., 1996; Semba et al., 1998). Indeed, depression was the only withdrawal symptom that reliably predicted relapse in abstinent smokers (Hughes, 2007). Thus nicotine-produced antidepressant effects might ease withdrawal effects and perpetuate relapse to smoking. The effects of nicotine on 5-HT systems could also influence addiction by directly modulating the functioning of DA neurons via 5-HT receptors (Carey et al., 2004; De Deurwaerdere et al., 1998, 2004; De La Garza and Cunningham, 2000; Di Matteo