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Nicotine Addiction: Role of the Nicotinic Acetylcholine Receptors Genetic Variability in Knowledge, Prevention and Treatment

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1. Introduction

In 1988 the US Surgeon General's report stated that tobacco use, in any form, is addicting as a result of its nicotine content and defined the processes determining tobacco addiction as "similar to those that determine addiction to drugs such as heroin and cocaine" (U.S. Surgeon General, 1988). Tobacco smoking has been classified by the WHO International Classification of Diseases (ICD-10) under the "Mental and behavioural disorders" (F00-F99 (<http://apps.who.int/classifications/apps/icd/icd10online/>)). Continuous use of nicotine induces adaptive changes in the CNS leading to tolerance, physical or physiological dependence, sensitization, craving, reward and relapse. Drug addiction has been defined by Koob (2008) as "a chronically relapsing disorder characterized by compulsive drug use and loss of control over drug intake". Indeed Koob (2008) proposed that addiction includes three different stages, which are: "preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect". As a final result chronic use of nicotine produces 'tolerance', an occurrence that reduces the effect of a drug given dose (Fig. 1.).



Fig. 1. Steps signals involved in the circuit of nicotine addiction (adapted from Russo, 2011).

Cessation of tobacco use determines a withdrawal syndrome, characterized by agitation, irritation, frustration or anger, concentration difficulty, depressed mood, anxiety, restlessness, decreased heart rate and increased appetite or weight gain (Benowitz, 2010; Perkins, 2002; Shiffman et al., 2004). These symptoms occur after four to twelve hours, peak after one week and decrease progressively over time (Perkins, 2002). Nicotine addiction is sustained by the individual positive effects experienced during smoking, and by the wish to hold off the negative symptoms of nicotine withdrawal. Thus, episodic and repetitive doses of nicotine are indispensable to maintain normal levels of functioning. Moreover, stress conditions, processes concerning consciousness, evaluation and response to negative, threatening or, challenging events or stimuli have been found to exacerbate nicotine withdrawal symptoms and increase vulnerability to relapse (Morissette et al., 2007).

2. Neurochemistry of Nicotinic receptor (nAChR)

The functional properties of nicotine are related to its interaction with the nicotine receptors (nAChR). nAChR are acetylcholine gated ion channels consisting of homo- or heteropentamers subunits arranged symmetrically around a membrane perpendicular axis, outlining the ionic hole (Russo et al., 2006; Taly et al., 2009) (Fig. 2).

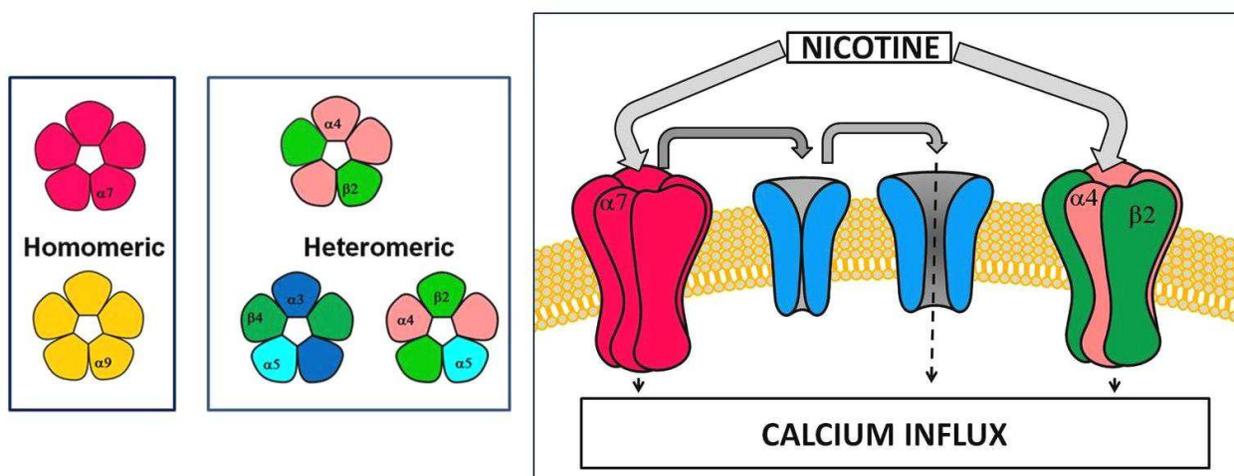


Fig. 2. Nicotinic Receptors. nAChR consist of homo- (e.g. $\alpha 7$ or $\alpha 9$, non the left) or heteropentamer (e.g. $(\alpha 4)_3(\beta 2)_2$, $\alpha 5(\alpha 3)_2(\beta 4)_2$, $\alpha 5(\alpha 4)_2(\beta 4)_2$), composed of the various subunits ($\alpha 1$ – $\alpha 10$; $\beta 1$ – $\beta 4$) that are arranged symmetrically around an axis perpendicular to the membrane, thus delineating the ionic pore. The α subunits are distinguished by the presence of adjacent (vicinal) Cysteine residues in loop C, and this originally defined α subunits as agonist-binding subunits. The homomeric $\alpha 7$ nAChR is a special case, since having five agonist-binding sites per receptor can bind from two to five molecules of agonist. $\alpha 7$ -nAChR utilizes multiple calcium amplification pathways to efficiently raise the intracellular calcium levels by subsequent activation of voltage-gated calcium channels as well as calcium release from the endoplasmic reticulum (Russo et al., 2006; Taly et al., 2009).

The composition and stoichiometry of the pentamer determines receptor pharmacology, cations selectivity, desensitization kinetics and spatial distribution. Receptors containing $\alpha 4$ and $\beta 2$ subunits are the most abundant in the CNS accounting for the majority of nicotine high affinity binding sites (Flores et al., 1992; Schoepfer et al., 1988). It has been shown, by

pharmacological and ligand-binding experiments, that nAChR containing the $\beta 2$ -subunit ($\beta 2^*$ nAChR, the asterisk indicates the possibility of other subunits to be incorporated in the receptors) bind to nicotine with high affinity (Changeux et al., 1998). $\beta 2$ -containing nAChR, which have been implicated in nicotine self-administration (Picciotto et al., 1998), do not influence the onset of nicotine withdrawal symptoms (Salas et al., 2004). Evidence shows that acute nicotine self-administration is absent if the $\alpha 4^*$ receptors are deleted (Marubio et al., 2003; Pons et al., 2008). Activation of $\alpha 4$ nAChR is sufficient to sustain nicotine-induced reward, tolerance and sensitization (Tapper et al., 2004). Since the $\alpha 3$ and $\alpha 5$ subunits are coexpressed within $\alpha 4$ in the medial habenula (MHb), in the interpeduncular nucleus (IPN) and in the peripheral ganglia, it is likely that $\alpha 3^*$ and $\alpha 5^*$ nAChR may be involved in the mechanisms of nicotine withdrawal. It has been shown that $\alpha 6\beta 2^*$ nAChR expressed in the VTA (ventral tegmental area) are necessary for the effects of systemic nicotine on DA (dopamine) neuron activity and DA-dependent behaviours, such as locomotion and reinforcement. It was proposed that both $\alpha 6\beta 2$ and $\alpha 4\beta 2$ receptors are necessary for (at least some of) the effects of nicotine on the DA system. In the brain, the homomeric $\alpha 7$ subtype is the most abundant and widespread nAChR (Breese et al., 1997; Quik et al., 2000), being involved in the modulation of glutamatergic and cholinergic neurotransmitter release, in the synaptic plasticity, in the regulation of neuronal growth, in the differentiation and survival, in the regulation of calcium-dependent gene expression and in the mediation of circuit excitability (reviewed in Gotti & Clementi, 2004). New data support a model in which the $\alpha 7$ nAChR, found on glutamate terminals, increases glutamate release contributing to presynaptic facilitation and synaptic plasticity and enhancing dopamine release from neighbouring boutons (Livingstone et al., 2010). The regulation of the nAChR is linked to their intrinsic property of being allosteric receptors. (Changeux & Edelstein, 2005). Thus nAChR are susceptible to desensitization and inactivation following, or in some cases independent of, channel opening (Giniatullin et al., 2005). Desensitization represents a decrease or loss of biological response after prolonged or repetitive stimulation by an agonist, such as nicotine, or a neurotransmitter. Indeed, when nicotine is continuously applied, nAChR become 'desensitized' (i.e. temporarily inactive) (Katz & Thesleff, 1957; Quick & Lester, 2002). The sensitisation-desensitization is correlated to the property of nAChR to increase their expression (upregulation) when exposed to nicotine (Vallejo et al., 2005; Gahring et al., 2010). Subtypes containing $\alpha 2$, $\alpha 3$ and $\alpha 5$ are not up-regulated by chronic nicotine administration (Mao et al., 2008; Marks et al., 1992), whereas $\alpha 4$ - or $\beta 2$ -containing nAChR (Tapper et al., 2004; Nashmi et al., 2007), containing subunits are up-regulated following repeated nicotine administration (McCallum et al., 2006). $\alpha 7$ upregulation occurs at higher nicotine concentrations than are required to increase $\alpha 4\beta 2$ nAChR (Pauly et al., 1991; Rasmussen & Perry, 2006; Kawai & Berg, 2001). Up-regulation of $\alpha 6$ -containing receptors, after nicotine administration, is a process which less clear, since studies report either upregulation (Parker et al. 2004), down-regulation (Lai et al., 2005; Perry et al., 2007) or no change (Drenan et al., 2008; McCallum et al., 2006).

3. Mechanism of nicotine addiction

Although the molecular mechanisms leading to and maintaining NA are not completely understood, they involve the regulation of brain monoamines levels and in particular DA (Benowitz, 2010; Changeux, 2009). Nicotine stimulates those nAChR placed principally in the ventral tegmental area, in the nucleus accumbens and in the pedunculopontine and

laterodorsal tegmental nuclei, important neuronal structures of the mesolimbic reward pathway (Brunzell et al., 2009; Dani, 2003; Exley & Cragg, 2008; Sharma & Brody, 2009; Schiltz et al., 2005). It has been proposed that the change from voluntary drug use to a more habitual and compulsive drug use, corresponds to a transition, at the neural level, from prefrontal cortical to striatal control, as well a progression from ventral to more dorsal domains of the striatum, involving its dopaminergic innervation (Everitt & Robbins, 2005). These neural transitions may themselves depend on the neuroplasticity in both cortical and striatal structures that is induced by chronic self-administration of drugs. Several nAChR subtypes such as: $\alpha 4\alpha 6\beta 2\beta 3$, $\alpha 4\beta 2$, $\alpha 4\alpha 5\beta 2$, $\alpha 6\beta 2\beta 3$ and $\alpha 6\beta 2$ are expressed on dopamine nerve terminals (Grady et al., 2007). Converging indication proposes that the dopaminergic system is important in mediating the pleasurable feelings of reward when activated by nicotine (Soderpalm et al., 2000; Zoli et al., 2002). It has been hypothesized that exposure to nicotine may initially increase the firing of ventral tegmental area GABAergic neurons through $\alpha 7$ nAChR activation, followed by $\alpha 7$ nAChR desensitization, that leads to the disinhibition and firing of DA neurons. This latter event might be also enabled by a more prolonged activation of the $\alpha 7$ nAChR expressed on glutamatergic terminals (Wonnacott et al., 2005). At the molecular level, several studies have suggested that ERK1/2 activation followed by phosphorylation of Cyclic AMP Response Element Binding protein (CREB) at Ser¹³³ and the activity of Fos gene are highly involved in many forms of experience dependent plasticity, such as long-term potentiation (LTP; Wu et al., 2007). Δ FosB, a long-lived truncated isoform of the FosB protein, accumulates within the striatum of rats treated repeatedly with either cocaine or nicotine, for several weeks and suggesting a sustained molecular change initiated by drug experience (Nestler, 2001), although not sufficient to account for the perseverance of drug dependence. CREB may play an important role in the rewarding and reinforcing effects of many drugs of abuse (Nestler, 2001, 2002), since pCREB is required in the NAc to establish nicotine-conditioned place preference (CPP) in mice (Brunzell et al., 2009).

4. Genetic of nicotine addiction

Meta-analysis of studies on twins showed that both genes and environment are important in smoking-related behaviours, with an estimated mean heritability of 0.50 for smoking initiation and 0.59 for nicotine dependence (Li et al., 2003). In women, genetic factors have a larger role in initiation than in persistence, whereas the opposite is observed in men (Li et al., 2003; Madden et al., 1999). Recent genome-wide association studies (GWAS) have shown that the CHRNA5-A3-B4 region, on chromosome 15q24-25.1, encoding the $\alpha 3$, $\alpha 5$ and $\beta 4$ subunits, is strongly associated with nicotine dependence, as well as alcohol and cocaine dependence and lung cancer susceptibility (Amos et al., 2008; Amos et al., 2010; Bierut, 2010; Caporaso et al., 2009; Saccone et al., 2010; Spitz et al., 2008; Thorgeirsson et al., 2008). One of the strongest associations within the 15q24-25.1 region is the rs16969968, located in exon 4 of CHRNA5, which causes an amino acid substitution from an aspartic acid (D) to asparagine (N) (missense mutation) (D398N). This change reduces the $\alpha 4\beta 2\alpha 5$ receptor function (Saccone et al., 2007), as found by *in vitro* functional studies, which showed that $\alpha 4\alpha 5\beta 2$ receptors, containing the N substitution, exhibited a weaker response to nicotine compared to the D variant in $\alpha 5$ (Bierut et al., 2008). Other nAChR gene variants associated to ND are reported in Table 1.

Gene	SNP	Chromosome number/ position (base pairs)	Major/Minor Allele
CHRNA3	rs1051730	15/76681394	C/T
CHRNA3	rs11637630	15/76686774	A/G
CHRNA3	rs3743078	15/76681814	C/G
CHRNA3	rs578776	15/76675455	C/T
CHRNA3	rs7177514	15/76694461	C/G
CHRNA3/B4	rs8023462	15/76701789	C/T
CHRNA4	rs1044394	20/61452529	C/T
CHRNA4	rs2236196	20/61448006	A/G
CHRNA4	rs2273504	20/61458505	A/G
CHRNA4	rs6122429	15/76701810	C/T
CHRNA5	rs16969968	15/76669680	G/A
CHRNA5	rs17486278	15/76654537	A/C
CHRNA5	rs2036527	15/7663870	C/T
CHRNA5	rs569207	15/76660174	GA
CHRNA5	rs637137	15/7661031	T/A
CHRNA5	rs8034191	15/45468658	G/A
CHRNA6	rs1072003	8/42729008	C/G
CHRNA6	rs2304297	8/42725148	C/G
CHRNA6	rs892413	8/42727356	A/C
CHRN B2	rs2072658	1/152806850	A/G
CHRN B2	rs2072660	1/152815345	C/T
CHRN B2	rs2072661	1/152815504	A/G
CHRN B3	rs13280604	8/ 42678742	A/G
CHRN B3	rs4950	8/42671789	C/T
CHRN B4	rs1948	15/76704500	C/T

Table 1. Association Results for Significant SNP-Phenotype Associations 'Current Frequent Smokers', Reviewed in Russo, 2011.

5. Drugs in smoking cessation

The drugs for smoking cessation currently approved by the FDA (Hurt et al., 2009) include nicotine-replacement therapy (NRT), Bupropion and Varenicline. A Cochrane Database of Systematic Reviews 2009 (Hajek et al., 2009) that reassessed different randomized or quasi-randomized controlled trials of relapse prevention interventions, with a minimum follow up of six months, concluded that: (i) extended treatment with Bupropion is unlikely to have a clinically important effect; (ii) studies of extended treatment with nicotine replacement are needed and (iii) extended treatment with Varenicline may prevent relapse.

Varenicline [Systematic IUPAC name: 7,8,9,10-tetrahydro- 6,10-methano- 6H-pyrazino (2,3-h)(3) benzazepine (trade name Chantix), is an $\alpha 4\beta 2$ nicotinic receptor partial agonist and an $\alpha 7$ full agonist. The partial agonist activity induces modest receptor stimulation that attenuates the symptoms of nicotine withdrawal and inhibits the surges of dopamine release, responsible of the reinforcement and reward associated with smoking (Coe et al.,

2005; Foulds, 2006). Consequently, Varenicline suppresses the symptoms of nicotine withdrawal and reduces the pharmacologic reward from cigarette smoking (Rollema et al., 2007).

Bupropion [Systematic IUPAC name: (\pm) -2-(tert-butylamino)-1-(3-chlorophenyl)propan-1-one], initially approved by the FDA as an atypical antidepressant, belongs to the chemical class of aminoketones. Although its mechanism of action in smoking cessation is not completely understood, Bupropion is an inhibitor of DA and of nor-epinephrine reuptake; but it is also a weak antagonist of nicotinic receptors (Cryan et al., 2003; Fryer & Lukas, 1999;).

6. Drugs and nAChR gene variants

Although the association of nAChR variants and ND have been extensively studied, their role in drug therapy for smoking cessation is only pioneering. Conti et al. (2008) have identified two polymorphisms within the CHRNA2 (rs2072661 and rs2072660) having significant association with the abstinence rates, within a 6-month follow-up study on the effects of Bupropion in smoking cessation, in a placebo-controlled trial. Specifically, although a difference was found in the relapse rates at EOT (end of treatment), between carriers and non-carriers, for individuals who received Bupropion, there was a substantial increase in the relapse rates for those individuals carrying the minor allele, after they went off treatment. Follow-up analyses on the top SNP (rs2072661) indicated a role in the time to relapse within the 6-month follow-up period and an impact on withdrawal symptoms at TQD (target quit date). These two SNPs (rs2072661 and rs2072660) may be robust markers for identifying smokers most likely to relapse and those who may benefit from Bupropion therapy. In addition, these SNPs should be examined within pharmacogenetic studies of Varenicline for smoking cessation. There is evidence that smokers with a heterozygous TC genotype at SNP rs2236196 in CHRNA4 are more likely to maintain abstinence with nicotine nasal spray (Hutchison et al., 2007). Moreover, looking at rs2072661, smokers with the CHRNA2 GG genotype, could sustain more days of abstinence during the nicotine *versus* placebo patch week, compared with those with the AG or AA genotypes; regardless of patch condition, quitting on the 'target quit day' was more likely to occur in those individuals with the GG genotype versus AA/AG genotypes. Genetic associations were not observed for craving or withdrawal responses to nicotine *versus* placebo patch (Perkins et al., 2009). A recent research studied the association of the CHRNA3 gene (Tyr215Tyr or rs1051730) with quitting success in response to controlled short-term nicotine patch use in hospitalized individuals (De Ruyck et al., 2010). Point abstinence was considered, and it was found that neither this genetic polymorphisms, nor the interaction of genotype *versus* treatment group, were significantly associated with quit rates, at any of the considered time points. A recent smoking cessation pharmacogenetics study (King et al., 2012) analyzed 1476 consenting individuals (524 who take Varenicline; 440 Bupropion; 512 placebo). Among the subjects receiving Varenicline, two variants in CHRNA2 (rs3811450 and rs4262952) were significantly associated with continuous smoking abstinence. Interestingly Bupropion abstinence was associated with several SNPs within CYP2B6, one enzyme important for the metabolism of nicotine, including rs8109525.

Indeed, CYP2B6.8 (the K139E variant) is unable to metabolize Bupropion under normal turnover conditions (Zhang et al., 2011). All these data support the evidence that genetic loci

contribute to smoking cessation and therapeutic response. On the other hand, the response treatment to Varenicline *versus* Bupropion is associated with different genetic signals, implying that in future research clinically useful markers shall guide treatment decisions to achieve improved smoking cessation rates and reduction in smoking occurrence.

7. Conclusions

Recognition that tobacco use is driven by the “neurobiological diseases” of “nicotine dependence” and “nicotine withdrawal”, linked to specific nAChR variants, provides a rational basis for the development of drugs and treatment, as well as supporting the inclusion of pharmacotherapies for dependence and withdrawal, along with those targeting other medical disorders. In fact, the need to prevent public health and economic devastation, caused by tobacco use, supports treatment as a high priority in health care. Pharmacotherapy for tobacco dependence is also cost effective when compared to many widely supported forms of pharmacotherapy for diseases, such as hypertension and hypercholesterolemia, as well as preventive periodic screening such as mammography or Papanicolaou smears. Moreover, the nAChR SNPs examination is less expensive and less invasive than spiral-CT or PET-SCAN examination, as screening in smokers. Taken together, these data suggest that genetic susceptibility to nicotine dependence is linked to several nAChR subtype genes and variants, in each subunit gene, and that may give independent, as well as interactive, contributions to nicotine dependency at molecular level.

8. Acknowledgements

We apologize to the many contributors of this field whose work is important but that we were unable to cite here.

The painting shown in Figure 1 is the original work of Arch. Giulio Alzetta (1988, charcoal on paper) and has been included here with his permission.

Note: The Author states to disagree with the use of animals and animal models in research. As an author she is only responsible for the inclusion of the *in vitro* research and human studies reported here. She is a “conscientious objector”, according to the Italian Law: “Legge n. 413 del 12 ottobre 1993” entitled “*Norme sull'obiezione di coscienza alla sperimentazione animale*” (Italian Law on “conscientious objection to animal experiments”).

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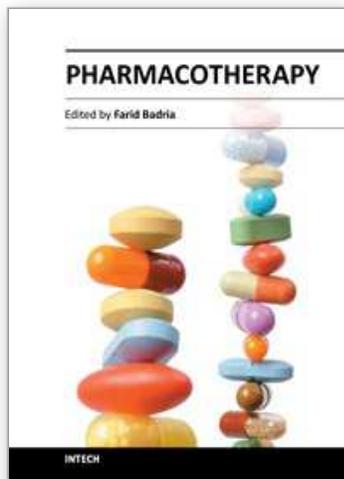
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The intent of this book is to provide an overview of current conceptualizations of Pharmacotherapy. The book focuses on three major areas; diagnosis, treatment, and prevention for a wide array of diseases; Cognitive and Psychological disorders (Schizophrenia and Nicotine addiction), Inflammatory disorders (New Chemical anti-inflammatory and Immunotherapy), updated antihypertensive therapy and healing of ulcers with venous origin. A separate chapter is dedicated to the rationality of drug use in earthquake injuries. The last chapter deals with Imaging of potential therapeutic or diagnostic agents in animal models in the early stage of research. We hope this book is useful to a wide range of people, from students first learning about Pharmacotherapy, to advanced clinicians and researchers.

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