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Review

Application of nicotine enantiomers, derivatives and analogues in therapy of neurodegenerative disorders

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Abstract

This review gives a brief overview over the major aspects of application of the nicotine alkaloid and its close derivatives in the therapy of some neurodegenerative disorders and diseases (*e.g.* Alzheimer's disease, Parkinson's disease, Tourette's syndrome, schizophrenia *etc.*). The issues concerning methods of nicotine analysis and isolation, and some molecular aspects of nicotine pharmacology are included. The natural and synthetic analogues of nicotine that are considered for medical practice are also mentioned. The molecular properties of two naturally occurring nicotine enantiomers are compared — the less-common but less-toxic (*R*)-nicotine is suggested as a natural compound that may find its place in pharmaceutical practice.

Keywords: Nicotine; Ageing; Alzheimer's disease; Parkinson's disease; Tourette's syndrome; Huntington's disease; Prion diseases; Free radical; Oxidative stress; Peptide; Reactive oxygen species; Nicotine addiction; Schizophrenia; Diabetes; Depression; Nicotinic receptor; Cytochromes P450

Contents

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1. Introduction

This mini-review does not attempt to be a complete summary of the current knowledge on the role of pyridine alkaloids in nature and the pathology of their harmful affects in human organism. We will address some data accumulated in the literature, which might have an impact on the medical applications of nicotine and its derivatives. Recent years have proved that some pharmaceutical agents, which have been originally designed to alleviate unpleasant side-effects accompanying tobacco smoking cessation, have a potential therapeutic effect in the major neurodegenerative, and neuropsychiatric diseases and disorders. There are several arguments that may favour the therapeutic use of nicotine and its analogs. The main one is a profound and still growing knowledge about nicotine metabolism and its physiological effects. It includes an enormous collection of data considering nicotine's therapeutic properties and side-effects. Almost none of bioactive compounds have been examined in such detail. There are already almost completely resolved nicotine delivery mechanisms, and well mastered methods of its analysis and drug formulation. The economic and social arguments are also of great importance. Huge natural resources of the raw material, tobacco, may be utilized to benefit society (Vagg and Chapman, 2005).

In this review quite a broad roundup of issues including physicochemical methods of nicotine analysis and isolation as well as some molecular aspects of nicotine pharmacology is given. Natural and synthetic analogues of nicotine that are considered for medical practice are also mentioned. The clinical trials and present day drug market reality are scrutinized as well. Especially we want to point to potential applications of the naturally occurring dextrorotatory enantiomer of nicotine, which seems to share a majority of the properties, except for the high level of toxicity, of the dominant levorotatory nicotine.

This review is by no means complete. Therefore for more comprehensive review, the reader is directed to several publications that appeared in the literature during the last two decades, from which we focused only on a few published during the last three years (Buccafusco and Terry, 2003; Czernin and Waldherr, 2003; Hecht, 2003; Hogg et al., 2003; Kelly, 2003; Kostrzewa and Segura-Aguilar, 2003; Lindstrom, 2003; Sellers et al., 2003; Grutter et al., 2004; Jarvis, 2004; McChargue et al., 2004; Pauly et al., 2004; Quik, 2004; Yildiz, 2004; Daly, 2005; Hukkanen et al., 2005; Malaiyandi et al., 2005; Shiffman et al., 2005; Terry et al., 2005; Vagg and Chapman, 2005; Wang and Sun, 2005; Punnoose and Belgamwar, 2006; Seidelin and Nielsen, 2006; Tutka et al., 2005). Some useful information could also be found on the websites of international non-profit organizations such as the Society for Research on Nicotine and Tobacco (www.srnt.org), the Society for Neuroscience (www.sfn.org), the World Health Organization (www.who.int) and its parts such as the International Agency for Research on Cancer (IARC) (www.iarc.fr), or the branches of various governments like the Official Documents Archive (UK) (www.archive.official-documents.co.uk), Technology Information, Forecasting and Assessment Council (INDIA) (www.tifac.org.in) and particularly National Center for Chronic Disease Prevention and Health Promotion (USA) (www.cdc.gov) where U. S. General Surgeon Reports are periodically published.

Current publications concerning basic and applied biological research are listed in the MEDLINE data base provided by National Library of Medicine (USA) at electronic address: www.nlm.nih.gov, which together with many other medicine-related subjects cover different aspects of biological activity of nicotine alkaloids.

2. Nicotine. Methods of isolation from tobacco and quantification in tobacco products and physiological fluids

Nicotine (*3-(1-methyl-2-pyrrolidinyl) pyridine*, see Fig. 1) and other natural pyridine alkaloids are present in tobacco leaves, cigarette smoke and smokeless tobacco products such as: chewing tobacco, and patches or chewing gums applied during tobacco smoking withdrawal (Dewick, 2002; Johnstone and Plimmer, 1959; Stedman, 1968; Schmeltz and Hoffmann, 1977; Armstrong et al., 1998).

The nicotine content of tobacco varies significantly with tobacco strain and the conditions of cultivation. Nicotine makes up about 90% of alkaloids presented in tobacco, which gives an

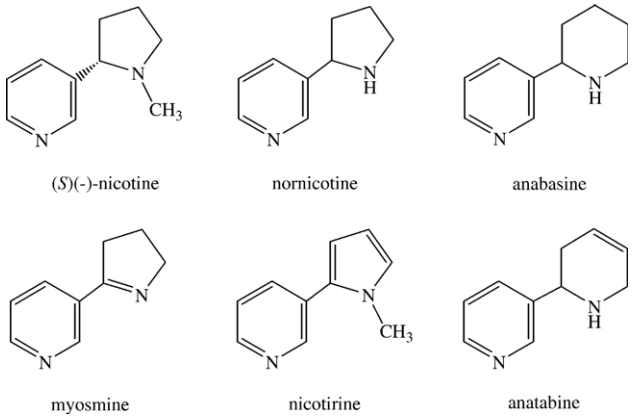

Fig. 1. Structures of major alkaloids present in tobacco. Nicotine is shown as the (*S*)-enantiomer, since it has the higher enantiomeric content in tobacco (Armstrong et al., 1998) (see below). The other alkaloids exist in tobacco as not very precisely defined mixtures of enantiomers, hence the isomeric form is not specified (Armstrong et al., 1999).

average of 1. 5% nicotine by weight (*ca*. 8. 4 mg of nicotine per one cigarette) (Benowitz et al., 1983a,b). The other major alkaloids in tobacco: are nornicotine, anabasine, myosmine, nicotyrine, and anatabine (shown in Fig. 1) making up 8 to 12% of the total alkaloid content of tobacco products (Piade and Hoffmann, 1980).

Commercially available nicotine is usually obtained by extraction of the dried leaves of tobacco plant (*Nicotinia tabaccum* and *N. rustica*). There are well established technologies that have been developed to produce nicotine and its salts (usually nicotine sulphate) from tobacco. In the first industrial technology (1953), tobacco powder is mixed with lime and water producing tobacco juice (Millen and Murphy, 1993). Nicotine is then extracted with kerosene and extract is treated with sulphuric acid to obtain nicotine sulphate solution containing 40% nicotine which can be easily converted to nicotine free base. Other commonly used technologies (1992) apply acidic ion exchange resins for recovery of nicotine from the aqueous extracts (Technology Information, Forecasting and Assessment Council, 2000; de Lucas et al., 1998), extraction with supercritical carbon dioxide (Zi-gang and Lin, 2004; Demirbas, 2001; Fischer and Jefferies, 1996), or ultrasound and microwave extraction techniques (Ng and Hupé, 2003). In spite of the efficient methods of alkaloid extraction from tobacco, in a typical tobacco industry, up to 20% of planted or farmed tobacco is wasted in the form of broken leaves and dust from manufacturing centres. Therefore, most of the current developments are aimed at utilizing the tobacco waste generated at farm stage and during processing of tobacco (Nicotine and its derivatives from tobacco waste, 2000).

Nicotine is so closely associated with tobacco that, to some extent, nicotine analysis is synonymous with tobacco analysis. In fact, nicotine is one of more than four thousands compounds that could be found in tobacco, many of which contribute to the flavour, aroma and also physiological effects making tobacco unique among the plants. However, the measurement of nicotine is the most important analytical determination made in tobacco. It is particularly difficult due to minor physicochemical differences between nicotine and the other alkaloids of tobacco (Gorrod and Peyton, 1999; Sangster and Stuart, 1965; Armstrong et al., 1999). Since the first measurements that were made gravimetrically (1929), the quantitative determination of nicotine in tobacco has been of great interest (Houston, 1952; Cundiff and Markunas, 1955; Willaman, 1952; Chamberlain et al., 1988; Gorrod and Peyton, 1999). The first official methods (AOAC, CORESTA) for the determination of nicotine in tobacco and commercial tobacco products were based on approaches that are not selective for nicotine (steam distillation, colorimetric and spectrophotometric measurements, titration with perchloric acid *etc.*). Since 70's, several automated procedures were developed for nicotine quantification due to the increasing requirements of the tobacco industry (Bowen and Barthel, 1943; Saunders and Blume, 1981; Burton et al., 1992). In recent years, the main studies undertaken to determine nicotine content have been based on near infrared reflectance measurement (Cowe et al., 1983; McClure et al., 1984; Davies et al., 1988), supported by advanced computational methodologies of data analysis (McClure et al., 1984; Davies et al., 1988; Hoy and McClure, 1989; Vardi et al., 1992), or by middle infrared techniques (Garrigues et al., 1998). Determination of nicotine in tobacco by circular dichroism gives additional possibility to distinguish between nicotine enantiomers (Atkinson et al., 1984). Nicotine content in tobacco can be successfully measured by nuclear magnetic resonance (NMR) methods. These methods give a unique opportunity to examine other compounds that can be found in tobacco, allowing precise measurements of enantiomeric content of natural material obtained from wild type and transgenic tobacco plants (Ratcliffe et al., 2001; Choi et al., 2004). There are few useful NMR methods for direct examination of tobacco leaves using solid-state ^{13}C and ^{15}N NMR cross polarization with magic-angle spinning methods (CPMAS NMR), the last one is presently the fastest method of determining nicotine content (Wooten, 1995; Ma et al., 2004). The chromatographic methods also offer the possibility of measurements of nicotine content in tobacco. Gas chromatography (GC) with nitrogen specific detector (Yang et al., 2002), high performance liquid chromatography (HPLC) method with UV detection (Saunders and Blume, 1981; Gorrod and Peyton, 1999) and reversed phase ion-pair liquid chromatography allow determination of nicotine in commercial tobacco products (Ciolino et al., 1999a,b,c). The use of solid-phase microextraction combined with gas chromatography/mass spectrometry (GCMS) allows the detection of nicotine and other most abundant alkaloids found in tobacco *i.e.* nornicotine, anabasine, and anatabine (Wu et al., 2002; Shen and Shao, 2006). One of the most important methods for accurate determination of nicotine in tobacco extracts is combined supercritical fluid extraction with ion mobility detector (SFC-IMD) (Wu et al., 1998). The detection limit here was lowered to the picogram level for nonselective monitoring and the subnanogram level for selective detection of nicotine. Since, not all aforementioned methods are practical for measurements of nicotine and its metabolites in physiological fluids, immunochemical methods have been developed. The sensitive and specific immunoassays for monitoring the level of nicotine and many of its metabolites in physiological fluids and following formation of products in *in vitro* and *in vivo* systems are available (Castro and Monji, 1986; Pickert et al., 1993; Dhar, 2004; Acosta et al., 2004; Langone et al., 1999; Isomura et al., 2005). Monoclonal stereospecific antibodies to nicotine and cotinine have been obtained and used to develop sensitive ELISA assays for these compounds. The methods are based on metabolic conversion of nicotine to cotinine, during which the reactive nicotine-$\Delta^{1'(5')}$-iminium cation is formed (see below) which has the potential of covalently binding with nucleophilic groups on macromolecules. Such complexes are detected immunochemically. The sophisticated methods of obtaining antibodies specific for each isomer of another nicotine metabolite nicotine *N*′-oxide (see below) have also been developed (Van, 1980; Langone and Van, 1982; Van et al., 1987, 1993; Obach and Van, 1990; Langone et al., 1973).

3. Molecular and physiological properties of nicotine

3.1. Absorption and bioavailability of tobacco products nicotine

Absorption of nicotine and the other alkaloids across biological membranes depends on pH (Armitage and Turner, 1970; Schievelbein et al., 1973). Nicotine is a tertiary amine, a weak base with a pK_a of 8. 02 (pK_{a2} = 3. 12) in aqueous solution at 25 °C (CRC Handbook, 2004). At physiological pH of blood (*ca.* 7. 4) about 69% of nicotine is in ionic form (protonated) and the rest remains nonionized. In its ionized state, such as in acidic environment of gastric fluid, nicotine does not cross membranes rapidly. Contrary to cigarette smoke, which has usually acidic pH (U.S. Department of Health and Human Services, 1988), chewing tobacco, snuff, and nicotine polacrilex chewing tobacco gums are of mild alkaline pH as a result of tobacco selection and/or buffering with additives by the manufacturer (U.S. Department of Health and Human Services, 1988). The alkaline pH, in which nicotine is largely nonionized, facilitates absorption of nicotine through mucous membranes. The rate of nicotine absorption from smokeless tobacco products depends on the product and the route of administration (Shiffman et al., 2005). When administrated through nasal mucosa, blood levels of nicotine rise almost as fast as those observed after cigarette smoking (Russell et al., 1980, 1981). The rate of nicotine absorption with the use of oral snuff and chewing tobacco is more gradual, since nicotine is poorly absorbed from the stomach due to the acidity of gastric fluid (Travell, 1960) but is well absorbed in the small intestine (Jenner et al., 1973), which has a more alkaline pH and a large surface area. In contrast to tobacco-smoke-nicotine absorbed through the lungs or oral and nasal mucosa, which reaches the systemic circulation without first passing through the liver, bioavailability of nicotine from the gastrointestinal tract (*i.e.* swallowed nicotine) is incomplete. Swallowed nicotine undergoes presystemic metabolism, thus after absorption into the portal venous circulation, nicotine is metabolized by the liver before it reaches the systemic venous circulation. Nicotine base can also be extensively absorbed through the skin (Faulkner, 1933; Gehlbach et al., 1975; Saxena and Scheman, 1985; Benowitz et al., 1987).

3.2. Distribution of nicotine in body tissues

The presence of hydrophobic pyridine and pyrrolidine rings in the nicotine molecule causes its low polarity and moderate hydrophobicity, which results in its good solubility in the environment of low polarity (Norton, 1940; Badgett, 1950; Millen and Murphy, 1994). Owing to these property, nicotine can readily pass into brain tissues crossing the blood–brain barrier (Olendorf, 1974; Oldendorf et al., 1993; Spector and Goldberg, 1982). Due to the same physical properties nicotine freely crosses the placenta and has been found in amniotic fluid and the umbilical cord blood of neonates (Van Vunakis et al., 1974; Luck et al., 1982; Hibberd et al., 1978). Sometimes, due to the lack of detoxication mechanism in a fetus, the fetal blood concentrations of nicotine may reach the level equal to or above that of the mother (Lichtensteiger et al., 1988). Distribution of nicotine in the organs depends on its affinity to particular tissue. Spleen, liver, lungs, and brain have high affinity for nicotine, whereas the affinity of adipose tissue is relatively low (Benowitz, 1986). Due to quite low affinity of nicotine to blood plasma proteins (Benowitz et al., 2006), more than 95% of nicotine remains there in the aqueous fraction of plasma. The animal studies have shown that the nicotine uptake into the brain is rapid, occurring within 1 or 2 min, and blood levels decline more slowly because of peripheral tissue uptake 20 or 30 min after administration (Olendorf, 1974; Schmiterlow et al., 1967; Stalhandske, 1970; Maziere et al., 1976). The distribution half-life, which describes the movement of nicotine from the blood and other rapidly perfused tissues, such as the brain, to other body tissues, is about 9 min (Feyerabend et al., 1985). Considering the data gathered so far the distribution kinetics rather than elimination kinetics (half-life, about 2 h) determines the time course of central nervous system actions of nicotine after its administration. The comprehensive review of pathways of nicotine absorption and its distribution in body tissues is shown in U. S. Department of Health and Human Services (1988).

3.3. Elimination of nicotine. Main pathways of nicotine metabolism

Renal excretion of unchanged nicotine, depending on urinary pH and urine flow, typically accounts for 5 to 10% of total elimination (Benowitz et al., 1983a,b; Rosenberg et al., 1980). Remaining nicotine is extensively metabolized, primarily in the liver, but also to a small extent in lungs (Jacob et al., 1988; Benowitz and Jacob, 1991; Hukkanen et al., 2005; Turner et al., 1975). However, it is worth to mention that respective enzymes that are able to metabolize nicotine have been found in various tissues including the brain (Miksys and Tyndale, 2002). The major metabolites of nicotine are cotinine and nicotine-*N*′-oxide (Fig. 2).

Studies on the molecular basis for formation of nicotine metabolites suggest that liver flavin-containing monooxygenases primarily catalyzes the nicotine-*N*′-oxide formation in a process leading mainly to *trans*-nicotine-*N*′-oxide (Cashman et al., 1992; Park et al., 1993; Parkinson, 2001). The oxides are stable under the metabolic conditions and seem to be not further

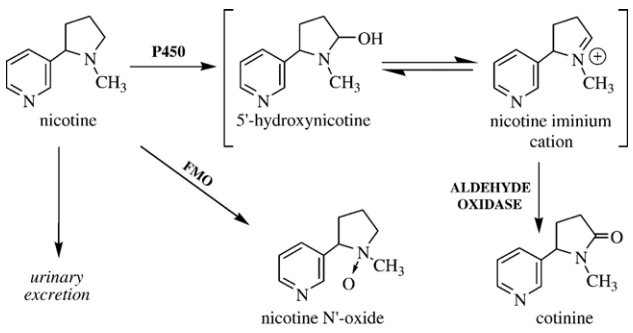

Fig. 2. Major pathways of nicotine metabolism.

metabolized and urinary excreted. Cotinine is formed in the liver in a multi-step process, the first of which involves oxidation of position 5′ of the pyrrolidine ring in a cytochrome P450-mediated process to an unstable intermediate 5′-hydroxynicotine, which exists in equilibrium with nicotine-$\Delta^{1'(5')}$-iminium cation (Murphy, 1973; Peterson et al., 1987). (The CYP2A6, a member of cytochrome P450 family of enzymes, seems to be most closely associated with nicotine metabolism (Gorrod and Schepers, 1999; Nakajima et al., 1996b; Nakajima et al., 1996a; Messina et al., 1997; Sellers et al., 2003)). In the next step, the iminium cation is metabolized by a cytoplasmic aldehyde oxidase to cotinine (Hibberd and Gorrod, 1983). Cotinine itself is also extensively metabolized, with less than 20% excreted unchanged in the urine (Benowitz et al., 1983a,b; Buccafusco and Terry, 2003). Several metabolites of cotinine have been reported (Jacob et al., 1988; Benowitz and Jacob, 1991, 1993; Hukkanen et al., 2005; McKennis et al., 1963; Dempsey et al., 2002, 2004; Langone et al., 1973; Zevin et al., 1997). The knowledge about the quantitative importance of these metabolites is not complete, however as for the other xenobiotics, each P450-mediated metabolic step will lead to the formation of a metabolite of higher polarity that facilitates urinary excretion. Cotinine and its metabolites account for 70 to 80% of nicotine metabolism in humans (Jacob et al., 1988; Benowitz and Jacob, 1991; Hukkanen et al., 2005; Turner et al., 1975). Nicotine is also metabolized to nicotine-glucuronide and several other minor metabolites not shown in Fig. 2 (Jacob et al., 1988; Benowitz and Jacob, 1991; Hukkanen et al., 2005; Turner et al., 1975; Byrd et al., 1992; Nakajima et al., 2002; Yamanaka et al., 2005; Caldwell et al., 1992).

3.4. The pitfalls of cytochrome P450-mediated metabolism. Formation of carcinogens

Usually, the process of xenobiotic metabolism by P450 is initiated by the introduction of a polar functional group on the compound thus decreasing its hydrophobicity. Completion of the solubilisation process proceeds by the conjugation of moieties such as glutathione, glucose or cysteine to the metabolite of the initial stage (Meunier et al., 2004). However, in some cases, during the process of xenobiotic elimination, reactive intermediates with toxic or carcinogenic properties may be formed (Erhardt, 1999; Sadeghi et al., 2001; Ioannides and Lewis, 2004). The generally accepted mechanism for the cytochrome P450 catalyzed α-carbon oxidation of tertiary amines involves initial transfer of an electron from the nitrogen lone pair to an electron-deficient heme-bound oxygen atom (Meunier et al., 2004). In the case of nicotine, this pathway leads to the aminium radical-cation intermediate (Mousa et al., 1985; Peterson et al., 1987; Peterson and Castagnoli, 1988; Lewis and Lake, 2002; Suffredini et al., 2005), which then undergoes a second one-electron oxidation that results in the net loss of a hydrogen atom from either the 5′- or 2′-carbon atom, or from the *N*-methyl group with the eventual formation of the corresponding iminium cations (Peterson et al., 1987; Peterson and Castagnoli, 1988; Lewis and Lake, 2002) (see Fig. 3).

Semi-empirical molecular orbital calculations indicated that the product ratio of nicotine metabolism can be directly related to HOMO electron densities on the relevant hydrogen atoms associated with oxidation sites in nicotine (Lewis and Lake, 2002). Molecular modelling of nicotine within the active site of CYP2A6 indicates that its enzymatic P450-mediated oxidation is strictly stereochemically controlled. The combination of hydrogen bonding and π–π stacking interactions orients the substrate for oxidation at the 5′-position. The alternative routes of P450-mediated nicotine metabolism require rotation of the pyrrolidine ring system. They are energetically less favourable than the formation of cotinine *via* 5′-oxidation (Lewis and Lake, 2002; Jones et al., 1993). However, they are experimentally observed-leading to the formation of nornicotine and 4-(3-pyridyl)-4-oxo-*N*-methybutylamine that are further metabolized. The later, being a product of 2′-oxidation, is the direct precursor to the tobacco-specific lung carcinogen NNK ((4-methylnitrosoamino)-1-(3-pyridyl)-1-butanone), which is believed to play a significant role as a cause of lung cancer in smokers (Hecht et al., 1978, 1998, 2000; Hecht, 2003; Wong et al., 2005; Hoffmann et al., 1985; Wong et al., 2005). The 4-(3-pyridyl)-4-oxo-*N*-methybutylamine is easily nitrosated, with an intrinsic rate constant similar to that of other of other secondary amines such as pyrrolidine (Caldwell et al., 1991; Caldwell et al., 1993; Mirvish, 1975). Nitrosation may occur under a variety of conditions (Halliwell and Gutteridge, 1999). For instance, nitric oxide (NO.) and peroxynitrite ($ONOO^-$) that are formed endogenously under conditions of chronic inflammation or infection (Winyard et al., 2000), may react with secondary amines — *via* N_2O_3, N_2O_4 and other intermediates — leading to endogenous nitrosamine formation. It appears that the carcinogenicity of nicotine metabolites has its origins in the ability of their hetero-aromatic molecules to stereospecifically bind to double stranded nucleic acids (Hecht, 2003). As a consequence of these interactions, the disturbance of translation process and genetic mutations is expected. Nicotine can also bind directly to some cellular receptors, leading to activation of protein kinase B, protein kinase A and other factors. This, in turn, can result in decreased apoptosis, increased angiogenesis and increased cell transformation (Hecht, 2003). Furthermore, the increased level of free radical and reactive oxygen species in the presence of nicotine derivatives may also lead to disadvantageous post-translational modification of proteins (Wetscher et al., 1995a,b; Newman et al., 2002; Tonnessen et al., 2000; Yildiz et al., 1998). CYP2A6 is involved in the metabolic activation of NNK, as well as in the metabolic activation of other potential carcinogens, including aflatoxin B, *N*-nitrosodiethylamine, and 1, 3-butadiene (Pelkonen and Raunio, 1995; Yamazaki et al., 1992). Therefore, the individual metabolic activity (Benowitz and Jacob, 1997), resulting mainly from genetic polymorphisms in the human CYP2A6 gene (Nakajima et al., 2000, 2001; Kwon et al., 2001; Yoshida et al., 2002; Yamanaka et al., 2004; Pianezza et al., 1998; Tyndale and Sellers, 2002; Xu et al., 2002; Howard et al., 2003a,b; Tutka et al., 2005), may have implications for cancer risk and susceptibly to nicotine dependence. For example, the lower CYP2A6 activity in Asian–Americans seems to be correlated

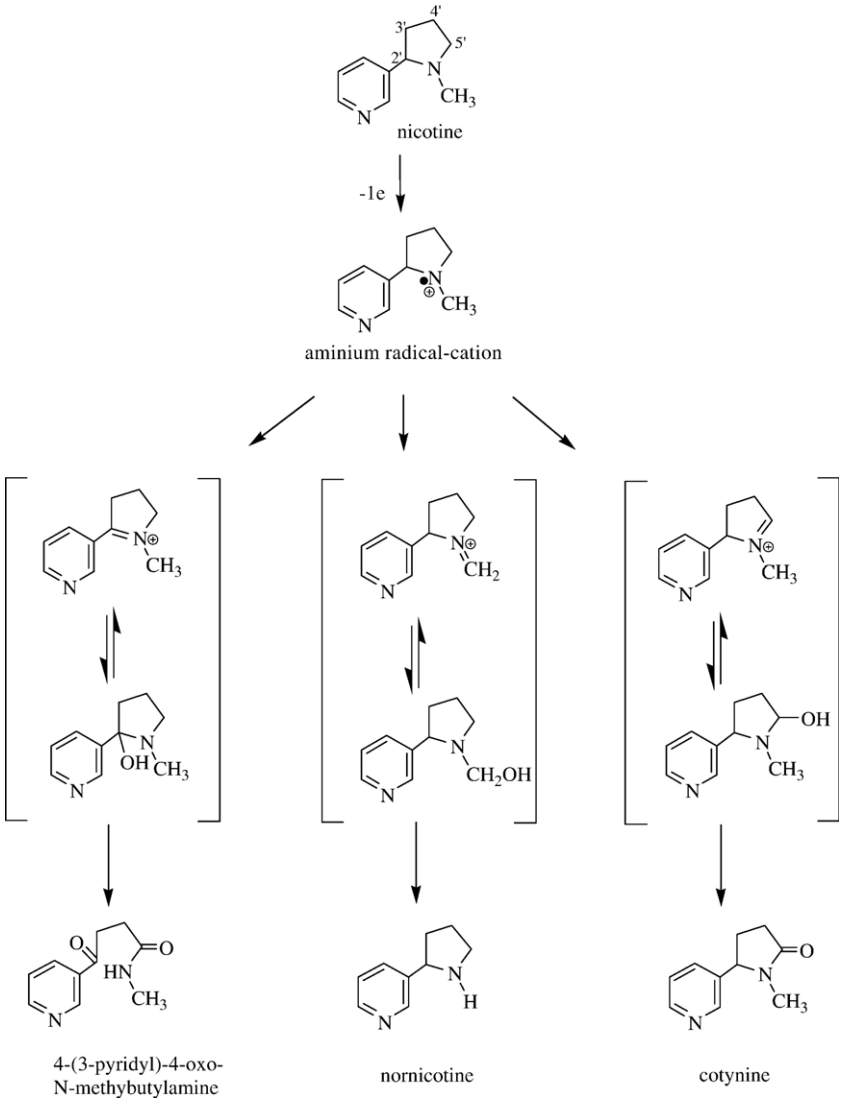

Fig. 3. Alternative pathways of P450-mediated nicotine metabolism.

with a lower risk of lung cancer from cigarette smoking as compared with white Americans (Benowitz et al., 2002a,b).

3.5. Nicotine toxicity and addiction, stimulation and desensitization of acetylcholine receptors

Historically, nicotine toxicity is difficult to differentiate from the toxicity of tobacco smoke, which is a complex mixture of chemicals that have been implicated in human diseases. The large group of nicotine metabolites is both cytotoxic and carcinogenic (Hecht, 2003; Hecht, 1998; Hoffmann et al., 1985; Carmella et al., 2000; Yildiz, 2004). Nicotine alone may contribute to tobacco-related disease, but direct prevalence has not yet been finally determined because nicotine is usually taken up simultaneously with a multitude of other potentially harmful substances that occur in tobacco smoke and smokeless tobacco products. Substantial nicotine exposure in long-term tobacco users affects many systems. Its relation to cardiovascular diseases, hypertension, reproductive disorders, cancer, and gastrointestinal disorders, including peptic ulcer and gastroesophageal reflux is of particular concern (U.S. Department of Health and Human Services, 1988).

In fact, the majority of aforementioned properties of nicotine is due to its agonistic interaction with one of two subtypes of cholinergic receptors (natively activated by acetylcholine) called therefore the nicotinic acetylcholine receptors (Lukas et al., 1999; Sharples and Wonnacott, 2001; Albuquerque et al., 1997; Lloyd and Williams, 2000a; Zhou et al., 2002; Bikádi and Simonyi, 2003; Celie et al., 2004). The nicotinic acetylcholine receptors are prototypes for the family of pentameric ligand-gated ion channels — structurally related to $GABA_A$ and $GABA_B$, 5HT, and glycine receptors (Le et al., 2002a,b). They consist of homo- or heteropentamers of homologous subunits, with an N-terminal ligand binding domain and a C-terminal transmembrane domain. These domains form 2–5 binding sites at selected subunit interfaces (Le et al., 2002a,b). The ligand binding site is characterized by the presence of aromatic hydrophobic residues that are contributed by two neighbouring subunits and a disulphide bond between two adjacent cysteine residues. The nicotinic acetylcholine receptors respond to

agonist binding by a single ion channel opening (Le et al., 2002a,b; Belluardo et al., 2004; Paterson and Nordberg, 2000; Piccotto et al., 2000; Sharples and Wonnacott, 2001; Le and Changeux, 2001). So far, the physical nature of nicotine binding to the receptors is not definitely resolved, and the nicotine affinity varies with different types of the receptor subunit (Piccotto et al., 2000; Levin, 2002). The nicotinic acetylcholine receptors containing the β2 subunit combined with various α subunits have the highest affinity for nicotine in contrast to those containing β4 subunit combined with various α subunits, which have 10–100 times lower affinity for nicotine (Piccotto et al., 2000). Moreover, the manners of nicotine binding to nicotinic acetylcholine receptors are different for different agonists of the receptors. The agonist-binding site interaction usually combines π–π and cation–π-type interactions together with hydrogen bonding (Graton et al., 2003).

For instance, the experiments with mutant nicotinic acetylcholine receptors where unnatural amino acids were incorporated using *in vivo* nonsense suppression methods, combined with *ab initio* quantum-chemical modelling for simple model of binding site of the α subunit have been performed. The results have shown that acetylcholine makes a cation–π interaction with Trp α149 whereas nicotine employs a hydrogen bond to a backbone carbonyl in the same region of the agonist-binding site (Cashin et al., 2005). That is in line with previous crystallographic studies showing employment of hydrogen bond in the binding of nicotine by acetylcholine binding protein (Celie et al., 2004; Le et al., 2002a,b; Grutter et al., 2004; Schapira et al., 2002; Bikádi and Simonyi, 2003). However, it has to be noted that acetylcholine binding protein is not a neuroreceptor, and shares only 20–24% sequence identity with nicotinic acetylcholine receptors α subunits. Additionally, the crystal structure of acetylcholine binding protein most likely represents the desensitized state of the receptor. The profound difference between the way of nicotine binding and the binding of native neurotransmitter-acetylcholine suggested that agonists of the nicotinic acetylcholine receptor could fall into two classes. They would be term "cholinergic", binding like acetylcholine, and "nicotinic", binding like nicotine (Cashin et al., 2005). That may help to understand distinctive differences of the affinity of different agonists to different subtypes of nicotinic acetylcholine receptors.

Since different subtypes of nicotinic acetylcholine receptors are found in a variety of organs, their stimulation produces quite different results in different tissues. Nicotine produces a complex pattern of mixed sympathetic and parasympathetic responses. The stimulation, desensitization and upregulation of nicotinic acetylcholine receptors by nicotine seem to be responsible for a plethora of physiological effects including psychomotoric (Grottick et al., 2003) and cardiovascular effects (Benowitz, 2003; Chadman and Woods, 2004; Zhang et al., 1998; Benowitz et al., 2002a,b; Pittilo, 2000; Czernin and Waldherr, 2003; Haass and Kubler, 1997), and nicotinic addiction (Yildiz, 2004; West, 2002b; Nomikos et al., 2000; Dani and de Biasi, 2001; Craig and Stitzel, 1997).

Nicotinic acetylcholine receptors are widely distributed throughout the human central nervous system, where they respond to acetylcholine and modulate neuronal excitability and synaptic communication, mediating a complex range of excitatory and inhibitory effects. Therefore, the actions of nicotine on the human central nervous system are the result of composite stimulatory and depressant effects. These can include tremors, convulsions, respiratory stimulation or depression, and release of antidiuretic hormone from the pituitary (Craig and Stitzel, 1997). As we mentioned before, the nicotinic acetylcholine receptors are structurally diverse and have varied roles. Presynaptic and preterminal nicotinic acetylcholine receptors enhance neurotransmitter release. Postsynaptic and somal nicotinic acetylcholine receptors mediate a small proportion of fast excitatory transmission and modulate cytoplasmic second messenger systems. At a synapse in the central nervous system, which is about 1 μm in diameter, acetylcholine is delivered by the presynaptic terminal at a concentration of about 1 mM for a couple of ms before it is hydrolyzed by acetylcholinesterase. This rapid pulse of agonist causes synchronized activation of nearby nicotinic acetylcholine receptors with little or no desensitization. Nicotine delivered from tobacco-related products arrives much more slowly at a concentration near or below 0.1 μM, and is present much longer (even up to several tens of minutes) in part because nicotine is not hydrolyzed by acetylcholinesterase (Buisson and Bertrand, 2001; Silman and Sussman, 2005; Ballard et al., 2005). This longer exposure to a low concentration of nicotine favours desensitization. A slow application of a low agonist concentration can cause some desensitization without activation because the desensitized conformation of the nicotinic acetylcholine receptor has a higher affinity for agonist than the resting or open conformation (Dani and de Biasi, 2001; Quick and Lester, 2002). Although the mechanism of nicotinic addiction is not completely understood, a part of nicotine's addictive power is attributable to actions upon the dopaminergic systems, which normally help to reinforce rewarding behaviours. Nicotine activates and desensitizes nicotinic acetylcholine receptors, and both processes contribute to the cellular events that underlie nicotine addiction. Nicotine, like many addictive drugs, elevates dopamine in the nucleus accumbens, and that elevation reinforces drug use (Dani and de Biasi, 2001; Kenny and Markou, 2001; Piccotto et al., 2000). Nicotine administration increases the circulating levels of insulin-antagonistic hormones (*i.e.* catecholamines, cortisol, and growth hormone), leading to hyperinsulinemia and insulin resistance increasing risk for diabetes (Eliasson et al., 1996; Eliasson, 2003).

3.6. Effects of nicotine in neurodegenerative and neuropsychiatric diseases and disorders

Numerous behavioural, epidemiological and molecular biology studies suggest that some symptoms and ailments accompanying the impairments of nicotinic acetylcholine receptors in neurodegenerative diseases, schizophrenia and depression might be alleviated by the administration of nicotine or the other agonists of the receptors. These compounds may act through receptor-mediated mechanisms and through non-receptor-mediated mechanisms as well. Historically, the affinity

of nicotine to nicotinic acetylcholine receptors caused isotopically labeled nicotine to be one of the primary drugs used to identify the receptors in the brain. It has allowed the diagnosis of neurodegenerative nicotinic acetylcholine receptor-associated diseases *e.g.* Alzheimer's disease (Nordberg, 1993; Leslie and Altar, 1988; Davenport, 2005; Sihver et al., 1999a,b,c).

One of the recognized pathologies in the brains of Alzheimer's disease patients is a loss of neurons in the basal forebrain complex that provides cholinergic input into neocortex (Piccotto et al., 2000; Court et al., 2001; Kihara and Shimohama, 2004; Sabbagh et al., 1998; Wevers and Schroder, 1999; Oddo and LaFerla, 2006; Nakamura et al., 2001; O'Neill et al., 2002). Receptor binding studies on post-mortem Alzheimer's disease brains have also shown a reduction of high-affinity nicotine binding, suggesting that β2 subunit-containing nicotinic acetylcholine receptors are lost in these patients (Nordberg, 1994; Court et al., 2001; Léna and Changeux, 1998). Also the protein content of α4, α3, and α7 nicotinic acetylcholine receptors is reduced in Alzheimer's disease brains (Nordberg, 2001). Additionally, behavioural studies have shown upon nicotine treatment the improved performance of the test evaluating several forms of learning and memory. The effects of nicotine appear to be most robust for working-short term memory (Rezvani and Levin, 2001a). Stimulation of brains of Alzheimer's disease patients by nicotine treatment has been shown to attenuate the decline in some of the cognitive deficits symptomatic of the disease and particularly effective in reversing attentional deficits (Lawrence and Sahakian, 1995; Lawrence and Sahakian, 1998; O'Neill et al., 2002; Rezvani and Levin, 2001b; Levin and Rezvani, 2002; Levin et al., 2006). The molecular bases of these fortunate phenomena are still not fully understood (Piccotto and Zoli, 2002; O'Neill et al., 2002). One of many theories proposes that nicotinic treatment enhances production of nerve growth factor and its receptors in the central nervous system (Schorderet, 1995; Rattray, 2001; Terry and Clarke, 1994; Jonnala et al., 2002). In the central nervous system, nerve growth factor protein has a close relationship with the cholinergic system: nerve growth factor promotes cholinergic neuron survival after experimental injury, and maintains and regulates the phenotype of uninjured cholinergic neurons. Nerve growth factor has also a rapid neurotransmitter-like action regulating cholinergic neurotransmission and neuronal excitability. On the other hand, nerve growth factor might promote hyper-phosphorylation of tau protein. Tau protein is neuron-specific, microtubule-associated protein, which forms paired helical filaments when aberrantly phosphorylated (Garver et al., 1995). The hyper-phosphorylated tau-protein filaments (tangles) are another biochemical marker (s) of Alzheimer's disease (Johnson and Jenkins, 1996; LaFerla and Oddo, 2005; Sobow et al., 2004).

Nicotine is one of the agents, which, when administered directly to the hippocampus in rats, produces a long-lasting elevation of nerve growth factor production (Terry and Clarke, 1994; Hernandez and Terry, 2005). It has also been suggested that nicotine-induced upregulation of the receptors could result in an increase in the number of nicotinic acetylcholine receptors at the cell surface. Different mechanisms have been proposed such as *de novo* synthesis of new proteins (Wonnacott, 1990), incorporation of an internal pool of pre-existing receptors (Sloan et al., 1985b), or a decrease of the turnover of receptors (Peng et al., 1994). On the contrary, the results of experiments examining the consequences of long-term exposure to nicotine in K-177 cells expressing the major human brain α4β2 receptor suggest that chronic exposure to nicotine only temporary increases the fraction of high-affinity receptors (Buisson and Bertrand, 2001). There is still controversy over the role of the amyloidal β-peptide (one of the major hallmarks of Alzheimer's disease (Sobow et al., 2004)) in the neuronal loss found in Alzheimer's disease brains. Several different hypotheses which try to explain the amyloidal β-peptide endothelial and neuronal toxicity on the molecular level as well as the reasons of memory deficit in Alzheimer's disease have been presented. Some of them are presented in the review articles cited here (Butterfield, 2002; Butterfield and Lauderback, 2002; Ghiso and Frangione, 2002; Katzman, 1986; Kihara and Shimohama, 2004; Lynch et al., 2000; Mera, 1991; Miranda et al., 2000; Schöneich, 2002; Smith et al., 2000; Trzesniewska et al., 2004; Yokel, 2000; Buchet and Pikula, 2000; Dworakowska and Dolowy, 2000; Pogocki, 2003; Roy and Rauk, 2005; Schoneich, 2005). It has been reported that the amyloidal β-peptide, especially the fragment 1–42, binds to α7 nicotinic acetylcholine receptor, inhibiting α7 receptor-dependent calcium activation and influx, and acetylcholine release, which could explain the cognitive deficits of Alzheimer's disease (Wang et al., 2000a,b). Importantly, immunocytochemical studies on human sporadic Alzheimer's disease brains have demonstrated that the amyloidal β-peptide and α7 nicotinic acetylcholine receptor are both present in neuritic plaques and co-localize in individual cortical neurons. Amyloidal β-peptide and α7 receptor can be co-immunoprecipitated, suggesting that they are tightly associated. Receptor binding experiments have confirmed this association. Human neuroblastoma cells with α7 nicotinic acetylcholine receptor are killed by the amyloidal β-peptide, and nicotine and its analogue epibatidine have been found to inhibit this death (Kihara and Shimohama, 2004). Additionally, amyloidal β-peptide activates the mitogen-activated protein kinase (MAPK) cascade *via* α7 nicotinic acetylcholine receptor (Dineley et al., 2001). The amyloidal β-peptide-induced activation through α7 receptor might downregulate the MAPK-CREB phosphorylation system, which leads to the dysfunction of memory formation, since CREB, cAMP-regulatory element binding protein, is thought to be one of the most important molecular components for hippocampus-dependent memory formation in mammals. This alone suggests that blockade of the association between α7 receptor and the amyloidal β-peptide might be a strategy for the treatment of Alzheimer's disease (Newhouse et al., 2001). Nicotinic receptor stimulation inhibits the amyloidal β-peptide toxicity and glutamate toxicity (Kihara et al., 1997, 1998, 2001; Shimohama et al., 1996), and therefore nicotine could inhibit neuronal death, which would counter the progress of Alzheimer's disease pathogenesis. Additionally, nicotine can directly interact with the amyloidal β-peptide. Normally, in aqueous solution at physiological pH, the synthetic amyloidal

β-peptide readily aggregates and precipitates as oligomeric β-sheet structures, a process that occurs during amyloid formation in Alzheimer's disease. Application of circular dichroism and ultraviolet spectroscopy has shown that nicotine (*in vitro* and *in vivo*) and its major metabolite cotinine (*in vitro*) inhibit formation of amyloid plaques by the amyloidal β-peptide (Salomon et al., 1996; Nordberg et al., 2002; Moore et al., 2004). However, the PET studies have shown that cotinine do not have the ability to cross the blood–brain barrier to any significant degree (Halldin et al., 1992). The NMR studies demonstrate that nicotine binds to the 1–28 region of the amyloidal β-peptide when it is folded in an α-helical conformation. The binding primarily involves the $N–CH_3$ and $5'CH_2$ pyrrolidine moieties of nicotine and the histidine residues of the peptide (Salomon et al., 1996; Moore et al., 2004). Nicotine retards amyloidosis by preventing an α-helix → β-sheet conformational transformation that is crucial for the β-peptide amyloidosis (Salomon et al., 1996; Nordberg et al., 2002; Moore et al., 2004). Nornicotine, an alkaloid present in tobacco, and also one of major nicotine metabolites, has been found to covalently modify the β-peptide, leading to its reduced aggregation by catalysis of nonenzymatic glycation of lysine residue on the surface of the peptide (Dickerson and Janda, 2003). The covalent modification of the KLVFF sequence physically blocks a critical site in the formation of amyloid fibrils. Potential consequences of this reaction include reduced plaque formation and/or altered clearance of the peptide, as well as attenuated toxicity of soluble amyloidal β-peptide and its aggregates by modifying their native conformations (Pogocki, 2003, 2004; Butterfield and Kanski, 2002; Kanski et al., 2001, 2002; Dickerson and Janda, 2003). Importantly, from the chemical viewpoint the other tobacco-related alkaloids and nicotine metabolites, such as anabasine and anatabine-containing like nornicotine a labile hydrogen atom bonded to the pyrrolidine nitrogen, should be able to participate to analogous protein glycation processes. These results indicate that nicotine and some of its metabolites may effectively reduce the amyloidal β-peptide aggregation in the brain, and nicotinic drug treatment may be a novel protective therapy in Alzheimer's disease (Salomon et al., 1996; Nordberg et al., 2002; Dickerson and Janda, 2003; Moore et al., 2004; Hellstrom-Lindahl et al., 2004a,b; Liu and Zhao, 2004). However, it is probable that nicotinic interventions, effective at clearing amyloid, might be disadvantageous for the other Alzheimer's disease sequela. For instance it has recently been shown that nicotine can actually exacerbate the tau-protein pathology (Hellstrom-Lindahl et al., 2000; Oddo et al., 2005). On the other hand it may beneficially reduce oxidative stress accompanying Alzheimer's disease and the other neurodegenerative disorders. The pyridine ring of nicotine has electrophilic properties, and as such it may scavenge free radicals with rate constants near the diffusion limit (Ross et al., 1992). Nicotine could participate in the complexation of redox-active transient metals (Kang et al., 2004; Bridge et al., 2004). For example, (*S*)-nicotine complexes with Cu^{II} chloride form a distorted tetrahedral geometry around the Cu^{II} site of relatively high reduction potential ($E_{1/2}$ *ca.* −50 mV *vs.* AgCl electrode) (Kang et al., 2004). However, this potential is significantly lower than that of copper coordinated by the histidine and tyrosine residues of the β-peptide ($E_{1/2}$ *ca.* 550 mV *vs.* Ag/AgCl electrode (Huang et al., 1999)). Therefore, the complexation of copper by nicotine may prevent reduction of Cu^{II} to Cu^{I} thus consequently inhibits generation of hydroxyl radicals (.OH) and superoxide anion radicals ($O_2.^-$) in a Fenton-like process that has been hypothesized as important in the pathology of Alzheimer's disease (Lynch et al., 2000; Marlatt et al., 2004) and prion diseases (Turnbull et al., 2003).

Epidemiological studies have shown association of smoking with a lower occurrence of Parkinson's disease, the illness associated with prolonged failure of nigrostriatal dopaminergic system (Siderowf and Stern, 2003; Frucht, 2004). The nicotinic treatment appears to provide some undeniable benefits in Parkinson's disease (Quik, 2004). There are various mechanisms that have been proposed to explain the protective action of nicotine on dopaminergic system. They assume protection through receptor-mediated and non-receptor-mediated pathways as well. The receptor binding studies performed for Parkinson's disease brains have demonstrated substantial decline (up to 50%) of the nicotinic acetylcholine receptors population in the brain regions associated with memory and learning *i.e.* frontal and temporal cortex and hippocampus (Quik, 2004). The nicotinic acetylcholine receptors of α2–α6* subtype appears to be one of the main victims of nigrostriatal damage (Quik, 2004, 2006). Therefore, drugs such as nicotine that target the receptors, which decline with nigrostriatal damage might be useful (Quik, 2004, 2006). Nicotine stimulation of presynaptic nicotinic acetylcholine receptors in the dopaminergic system elevates dopamine release (Piccotto et al., 2000), whereby it can provide some symptomatic benefits in Parkinson's disease. For long-lasting protection, the mechanism of rebuilding of the receptors similar to that proposed for Alzheimer's disease may function here as well. Enhanced nicotine-evoked dopamine release might also attenuate nigrostriatal damage and reduce Parkinson's disease progression, since neurotoxins that cause parkinsonism may be selectively transported into neurons *via* the same uptake system as dopamine (Di Monte, 2003; Gorell et al., 1998). Therefore, nicotine therapy could reduce nigrostriatal damage by stimulating the release of dopamine that would compete with toxin for entry into the nerve terminal. With less toxin in the terminal, less nerve cell damage might be expected (Quik and Di Monte, 2001). So far it is not clear if the activation of α2–α6* nicotinic acetylcholine receptors subtype takes part in the signaling mechanisms that might subsequently lead to neuroprotection through inhibition of toxin-induced apoptosis, and/or increased expression of neurotrophic factors crucial for neuronal maintenance, survival and regeneration (Ryan et al., 2001; Dajas et al., 2001; Costa et al., 2001; Jeyarasasingam et al., 2002; Matarredona et al., 2001; Roceri et al., 2001).

While a major focus is on receptor-mediated protection, nicotine might also play a more direct role in Parkinson's disease relief. It could enhance elimination (Quik and Di Monte, 2001) or suppress the formation of toxins by altering monoamine oxidase activity (Soto-Otero et al., 2002; Obata

et al., 2002). Nicotine might also act as an antioxidant (Newman et al., 2002; Soto-Otero et al., 2002; Obata et al., 2002) and/or inhibit complex I of the electron transport chain, with a consequent reduction in the levels of reactive oxygen species (Cormier et al., 2001, 2003; Newman et al., 2002). Nicotine can attenuate morphological deficits in a contusion model of spinal cord injury and protect cultured spinal cord neurons by inhibiting apoptotic cascades (Garrido et al., 2001; Ravikumar et al., 2005). Recently has been shown a receptor-independent nicotine-mediated neuroprotective effect exerted by the interaction of nicotine with mitochondrial respiratory chain at the complex I site causing attenuation of mitochondrial permeability transition due to neurotoxins (Xie et al., 2005).

It has been hypothesized that nicotine could act by stimulating drug-metabolizing enzymes of the cytochrome P450 family that are present in dopaminergic regions of the brain (Howard et al., 2002; Howard et al., 2003a,b; Miksys et al., 2000; Lee et al., 2006; Miksys and Tyndale, 2002). Enzyme activation could enhance the metabolism of toxic agents, thus lowering their levels and reducing neuronal damage. Nicotine metabolites are also able to mediate neuroprotective effects presently attributed to nicotine. Cotinine exhibits cytoprotective properties in cultured cells through a non-receptor-mediated mechanism (Buccafusco and Terry, 2003). On the other hand, in the manner analogous to that suggested for amyloidal β-peptide in Alzheimer's disease (Dickerson and Janda, 2003; O'Neill et al., 2002), nornicotine could prevent aggregation of α-synuclein (a major component of Parkinson's disease plaques) and reduce Parkinson's disease pathology. Following this, one may hypothesize that nicotine might be protective for the other diseases characterized by the formation of protein-containing plaques and accompanied by the increased oxidative stress *e.g.* Huntington's disease (Borlongan et al., 1996), and prion diseases (Kim et al., 2001; Liberski and Jaskolski, 2002).

Existing investigations also indicate that nicotine and the other nicotinic agonists might serve as therapeutics agents for schizophrenia and Tourette's syndrome (Léna and Changeux, 1998; McEvoy and Allen, 2002; Levin and Rezvani, 2000; Smith et al., 2006; Punnoose and Belgamwar, 2006; Howson et al., 2004). By stimulating the mesencephalic dopaminergic system nicotine might compensate for the reduced activation in the frontal and prefrontal cortex (hypofrontality) observed in schizophrenia (Nisell et al., 1995). Nicotine has been found to reverse the cognitive deficits produced by some antipsychotic drugs applied in therapy of schizophrenia and depression (Levin et al., 1996, 2005; Addy and Levin, 2002; Rezvani and Levin, 2004; Rezvani et al., 2006). Therefore, the increased smoking among schizophrenics and persons under depression, including those under antipsychotic treatment (McEvoy et al., 1995), seems to be rationalized by spontaneous nicotine self-administration (Batel, 2000; Dalack et al., 1998; McChargue et al., 2004). However, there are epidemiological data standing against these beliefs (Srinvasan and Thara, 2002).

A synergy between nicotine and dopaminergic neuroleptics also exists in the treatment of Tourette's syndrome (Dursun et al., 1994; Erdmann and Schneider, 1996; Sanberg et al., 1997; Howson et al., 2004), which is a hyperkinetic disorder characterized by sudden, rapid, and brief motor and vocal tics (Shytle et al., 2003). The brain area involved in the pathogenesis of the Tourette's syndrome is very likely represented by the basal ganglia which would explain the involuntary movements present in this disorder. There are studies suggesting that nicotine stimulation reduces tics (Arevalo et al., 1992; Rickards, 1992; McConville et al., 1992; Silver and Sanberg, 1993; Dursun et al., 1994; Sanberg et al., 1997; Dursun and Reveley, 1997; Howson et al., 2004). It has been hypothesized that in Tourette's syndrome the beneficial action of chronically administrated low doses of nicotine is due to desensitization of presynaptic nicotinic acetylcholine receptors in the striatum that are responsible for dopaminergic release (Shytle et al., 1996). On the contrary, an abnormal long-lasting desensitization of certain types of the receptors has been described as a possible pathogenic mechanism for schizophrenia and autosomal frontal lobe epilepsy (Harris et al., 2004; Mihailescu and Drucker-Colín, 2000; De et al., 2000). However, there are reports showing that nicotine treatment may be beneficial to some individuals with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) (Willoughby et al., 2003).

4. Nicotine containing medications available on the market and nicotine analogues under investigation

The widespread impact of tobacco smoking addiction on modern society causes tremendous social and economical expenses. This, on one hand, creates a market for pharmaceuticals assisting smoking withdrawal and on the other, growing pressure on tobacco industry and academic science that leads to extensive search for nicotine analogues that are less harmful to the health of the smokers (West, 2001, 2002a; Vagg and Chapman, 2005).

4.1. Pharmaceutical forms of nicotine

Since the late 90's, there are several commercial products containing nicotine offered on the market. They are originally intended to reduce the psychological desire and physical cravings for tobacco thus helping people to give up smoking by reducing their withdrawal symptoms (Anderson et al., 2002; Tutka et al., 2005). Some of them are available on prescription, but the majority is offered over-the-counter. The medications are formulated for the effective administration through oral and nasal mucosa (chewing gum, chewable tablets, lozenge, nasal spray and nicotine inhaler) and through the skin (stick-on patches or films). The most popular method is the application of nicotine polacrilex well known as nicotine gum (Hughes, 1990) available on the market since 1996. It is one of the best recognized uses of ion exchange resins AMBERLITE™ IRP64, which complexes free-base nicotine (Leo Corporation, 1973). When used as the active pharmaceutical ingredient in nicotine chewing gum, nicotine is released in a controlled manner for absorption across the oral mucosa. Nicotine polacrilex is much more stable than pure nicotine, and can be produced with varying nicotine contents as required in the final product. The nicotine–resin complex (nicotine resinate) is the principal

ingredient of the nicotine chewing gums and lozenges currently marketed by a variety of companies. The products are offered in doses equivalent to 2 and 4 mg of pure nicotine. The chewing gums and lozenges are usually sold under the over-the-counter regulations. The other form of nicotine delivery that is available under the over-the-counter regulations, are transdermal (stick-on) skin patches (Palmer et al., 2006). This type of drug delivery device consists of a drug reservoir sandwiched between an occlusive back layer and a permeable adhesive layer that attaches to the skin. The drug slowly leaches out of the reservoir, passes through the skin, and then into the blood stream. The marketed products usually offer controlled-rate of nicotine delivery in the range 7–22 mg per 24 h. The other method of nicotine delivery is in the form of an aerosol. Nicotine nasal spray is aerosolized nicotine contained in a spray pump (Schneider et al., 1995). The nicotine is delivered to the user by spraying it into the nostrils, and is rapidly absorbed by the nasal membranes (Schneider et al., 1996a,b). Each actuation of the spray pump delivers a metered 50 μl spray containing approximately 0.5 mg of nicotine. This form of nicotine delivery was approved for use by the FDA in 1996. The newest (1998) nicotine replacement method to receive FDA approval is the nicotine inhaler (Schneider et al., 1996a,b; Hjalmarson et al., 1997). The nicotine inhaler is a thin, plastic cartridge that contains a porous nicotine plug in its base. By puffing on the cartridge, nicotine vapour is extracted and absorbed through the lining of the mouth. One cartridge will last for 20 min of continuous puffing and deliver 4 mg of nicotine; only 2 mg is actually absorbed. Both, nicotine nasal spray and inhaler are made available by prescription.

4.2. Nicotine analogues under investigation

Neuronal nicotinic acetylcholine receptors are being more often consider as targets for drug discovery (Holladay et al., 1997; Lloyd and Williams, 2000b; Sihver et al., 2000). There is an ongoing wide-ranging survey for new nicotinic acetylcholine receptors agonists. The pre-clinical and clinical screening encompasses compounds of natural origins (Daly, 2005; Daly et al., 2005; Andriamaharavo et al., 2005), semi-synthesized or bio-synthesized (Viegas et al., 2005; Walsh, 2003; Facchini and St-Pierre, 2005) using naturally occurring substrates, as well as new designed and synthesized artificial ones (Sihver et al., 1999b; Lin et al., 1999; Terry et al., 1992; Buccafusco et al., 2004; Tonder and Olesen, 2001). The knowledge on nicotinic acetylcholine receptor structures and function, and better understanding of rules governing structure–activity relationship, which has been accumulated mainly throughout the last two decades, allows design of drugs with precisely defined target such as a particular subtype of the receptors (Buccafusco, 2004). A plethora of very promising compounds has been examined, but so far less than 5% is expected to develop into pharmaceuticals. Below, we present the examples of nicotinic acetylcholine receptors agonists, which have a chance to develop into pharmaceuticals, some of them are currently under advanced clinical examination. Certainly, due to the intellectual property protection and commercial secrecy, the list will not be complete. Depending on characteristic structural fragments, nicotinic agonists can be divided into three groups: (i) nicotinoids (structurally close to nicotine), (ii) bicyclic compounds (structurally similar to anatoxin-A and epibatidine) and (iii) imidacloprid analogues (Tonder and Olesen, 2001). SIB-1508Y (altinicline, (*S*)-5-ethynylnicotine) is more potent and selective than nicotine at the human α4β2 receptors subtype, having effectiveness of *ca.* 160% that of nicotine for stimulating striatal dopamine release (Cosford et al., 1996). At present, SIB-1508Y is in clinical trials for the treatment of Parkinson's disease (Bleicher and Cosford, 1999). Similarly to nicotine, the (*S*)-enantiomer of 5-ethynylnicotine (SIB-1508Y) has 25 times higher affinity than its racemic mixture known as SIB-1765. SIB-1553A, an alkyl–aryl pyrrolidine related compound is a potent releaser of hippocampal acetylcholine and has a broad profile of activity in rodent and primate models of attention and memory dysfunction (Schneider et al., 1999; Lloyd and Williams, 2000b). SIB-1663 and its active isomer SIB-1926 are conformationally restricted analogues of nicotine that have very high affinities to α2β4 and α4β4 receptors and no remarkable affinity to forty other receptors including acetylcholine α4β2 receptors (Vernier et al., 1998; Rao et al., 2004). ABT-418 is a bioisostere of nicotine containing an isoxazole fragment which is a full agonist at the α4β2 receptors with improved selectivity of dopamine release stimulation and interaction with non-neuronal nicotinic acetylcholine receptors; it is 20 times less toxic than its analogue — epibatidine (Sacaan et al., 1996; Holladay et al., 1997). The first results of Alzheimer disease trials demonstrate that ABT-418 has some cognitive benefits (Holladay et al., 1997; Potter et al., 1999). Stereochemically, the (*R*)-enantiomer of ABT-418 has higher affinity than the (*S*)-one. Another nicotinic agonist, ABT-089 (Lin et al., 1997a; Sullivan et al., 1997; Decker et al., 1997), was selected for preclinical evaluation on the basis of its cognitive enhancing properties in monkeys, and it might have application for treating attention deficit disorder (Prendergast et al., 1998; Holladay et al., 1997; Koren et al., 1998; McGaughy et al., 1999). Enantiomeric affinities of ABT-089 for both (*S*)- and (*R*)-isomers are equal, but even small substituents on saturated nitrogen results in large differentiation (Abreo et al., 1996; Lin et al., 1997b). Epibatidine, an alkaloid isolated from the skin of the Ecuadorian frog *E. tricoloris* (Spande et al., 1992; Daly et al., Spande, and Garraffo, 2005; Daly, 2005), is a potent but nonselective nicotinic acetylcholine receptors agonist. Unlike nicotine, both enantiomers of epibatidine have similar functional activity and potency, and its usefulness is limited by its nonselective action, which results in a deleterious action on central nervous system responses and the respiratory system (Hama et al., 2001; Sacaan et al., 1996; Sihver et al., 1999a,b,c). Mecamylamine, a nicotinic acetylcholine receptors antagonist which has anomalous agonist-like activity at lower concentrations (Papke et al., 2001; Young et al., 2001), is the active pharmaceutical ingredient in Inversine® (mecamylamine hydrochloride, Targacept Inc.), the product in phase II clinical trial, and is approved by FDA for the treatment of severe hypertension and some cases of malignant hypertension. 3-(2, 4-dimethoxybenzylidene)anabaseine (GTS-21) is a partial agonist for rat α7 nicotine receptors with much lower efficacy for human α7 receptors. Since this drug improves memory-related performance, it is presently in a clinical trial for Alzheimer's

disease. The GTS-21 and its metabolite 4OHGTS-21 are long-lasting drugs; they appear to be more effective after 24 h than just after drug administration (Buccafusco, 2004).

Ispronicline (TC1734), that is a partial agonist at α4β2, produces long-lasting cognitive enhancement in rats after a single oral dose improving working and reference memory (Gatto et al., 2004). Similarly, (*S*)-*N*-methyl-5-[5-pyrimidinyl]-4-penten-2-amine (TC1827), which is a full agonist for α4β2 subtype receptors, shows long-lasting cognitive effects after elimination from the brain. RJR-2403 (transmetanicotine) is similar in potency to nicotine at α4β2 receptors, but it is up to 30 times less potent than nicotine in stimulating dopamine release. ABT-594, a 3-pyridyl ether, is equivalent in effectiveness to morphine as an analgesic agent and is up to 100 times more potent (Bannon et al., 1998). DBO-83, a 3, 8-diazabicyclo[3.2.1]octane derivative, also has analgesic activity and is a full agonist at α4β2, but lacks activity at neuromuscular junction nicotinic acetylcholine receptors (Holladay et al., 1998; Decker and Meyer, 1999). AR-R 17779 is a full agonist selective for the α7 receptors and is more potent than nicotine at this site. This compound has antianxiety activity, improves learning and memory, and does not substitute for nicotine in drug discrimination models (Levin et al., 1999; Van et al., 2004).

5. Biological properties of the (*R*)-nicotine enantiomer and the perspectives of its application as a therapeutic agent

Naturally occurring alkaloids, isolated from tobacco leaves, in most cases are optically active. In the case of nicotine, the natural product is dominated by the levorotatory (*S*) enantiomer (traditionally named L- or (−)-nicotine), which stereochemical formula is shown in Fig. 1, whereas, the content of the dextrorotatory (*R*)-enantiomer of nicotine usually does not exceed a few percent (Armstrong et al., 1998; Yildiz et al., 1998; Demetriou et al., 1993; Tang et al., 1998). The numerous studies have indicated that the pharmacological effects of (*R*)-nicotine are qualitatively similar to but quantitatively less potent than those of (*S*)-nicotine. Due to common physicochemical properties (pK_a, aromaticity, solvent accessible area *etc.*), both nicotine enantiomers will share the same basic absorption behaviour. The efficiency of the administration routes should be similar for both enantiomers. The ease of crossing biological barriers is expected to be identical as well.

On the contrary, since the enantiomers have different affinities in particular tissues, differences in distribution among organs are expected. Yet, the individual metabolic pathways and the amplitude of interactions with the acetylcholine receptors are the most prominent features differentiating both nicotine enantiomers. These factors are decisive for cytotoxicity and their therapeutic usefulness.

The acute toxicity and pharmacological effects of (*R*)-nicotine have been examined in several species of animals and compared with those of (*S*)-nicotine. The LD_{50}s for intravenous administration of (*R*)-nicotine have been *ca*. 18 times higher (6.15 mg/kg) than that of (*S*)-nicotine (0.33 mg/kg) (Shimada et al., 1984a,b). (*R*)-nicotine shows qualitatively the same effects as the (*S*)-isomer in the ganglionic or neuromuscular sites. The relative potency of the (*R*)-isomer has been approximately 0.06 in the case of rat blood pressure (elevation), approximately 0.2 in the cat superior cervical ganglion (stimulation and blockade) and approximately 1.0 in the neuromuscular junctions of the rat diaphragm (blockade) (Ikushima et al., 1982; Shimada et al., 1984a,b). In the adrenergic nerve terminals of the isolated rabbit pulmonary artery, where (*S*)-nicotine creates sympathomimetic effects by releasing norepinephrine from those terminals, (*R*)-nicotine does not produce such effects (Ikushima et al., 1982). Moreover, some inhibition of those effects caused by the (*S*)-isomer after administration of (*R*)-nicotine has been observed (Ikushima et al., 1982). In unanesthetized rhesus monkeys, EEG activity has not been influenced by the 64 μg/kg dose of intravenously administrated (*R*)-nicotine, while the same dose of (*S*)-nicotine has produced seizure-like waves (Shimada et al., 1984a,b). In anesthetized rats, (*R*)-nicotine has elevated the blood pressure and increased the heart rate with a potency of about one-eighth that of the (*S*)-isomer (Shimada et al., 1984a,b). (*R*)-nicotine elicited contraction of isolated rat ileum preparations, but with the potency of about one-tenth that of the (*S*)-isomer (Shimada et al., 1984a,b). Importantly, contrary to (*S*)-nicotine, (*R*)-nicotine treatment of the rat brains has not influenced their body weight since supposedly (*R*)-nicotine does not interact with *N*-methyl-D-aspartate receptors (Zhang et al., 1994).

The estimated average affinity of (*R*)-nicotine to nicotinic acetylcholine receptors is about ten times lower than that of (*S*)-nicotine (Sloan et al., 1985a; Khan et al., 1994a,b; Risner et al., 1988; Barlow and Hamilton, 1965; Zhang and Nordberg, 1993; Ikushima et al., 1982; Lu et al., 1999; Dwoskin et al., 1995; Funayama et al., 1995; Damaj et al., 1999; Marin et al., 1997; Lu et al., 1998; Bikádi and Simonyi, 2003; Sloan et al., 1985b). For example, saturation studies on binding characteristics of (*S*)- and (*R*)-nicotine to the rat brain P2 fraction, employing (*S*)- and (*R*)-tritium labeled nicotine, have indicated that the isomers bind to different very high and high-affinity sites since the binding density for (*S*)-[^{3}H]nicotine has been 10 times that for (*R*)-[^{3}H]nicotine. (Both isomers also bind to a low affinity site.) The isomers also appear to bind to a separate site which enhances binding at the (*S*)- and (*R*)-nicotine high-affinity sites (Sloan et al., 1983, 1984, 1985a, 1988). These results and similar experiments performed *in vivo* on the rat brains applying tritium-labeled (Zhang and Nordberg, 1993) and the ^{11}C-labeled (Nordberg et al., 1989) nicotine enantiomers suggest that (*R*)-nicotine may preferably bind to different subtypes of nicotinic acetylcholine receptors than (*S*)-nicotine. Thus, the mechanisms involved in the effects of (*R*)-nicotine and (*S*)-nicotine on the receptors may be slightly different. So far neither the capability of (*R*)-nicotine to desensitize nicotinic acetylcholine receptors nor the extent of its addictive power related to the stimulation of dopaminergic system is clear. Interestingly, behavioural studies have shown that the subjective hedonic effects among the smokers caused by (*R*)-nicotine are of an intensity comparable to that caused by the (*S*)-enantiomer (Thuerauf et al., 1999, 2000).

With some exceptions (Crooks and Godin, 1988; Cundy et al., 1984; Cundy et al., 1985; Nwosu et al., 1988; Nwosu and Crooks,

1988; Pool and Crooks, 1985, 1988), both nicotine enantiomers share a similar main metabolic pathway (Gairola et al., 1988; Carmella et al., 2000; Houdi et al., 1988; Nwosu et al., 1988; Zimmerman et al., 2004; Cashman et al., 1992; Nwosu and Crooks, 1988; Sandu et al., 2003; Jones et al., 1993). The overall metabolic rate has been measured for CYP101 (cytochrome P450cam) isolated from *Pseudomonas putida* (Jones et al., 1993). The rate of (*R*)-nicotine is *ca*. 1.4-fold faster than for (*S*)-nicotine, which is consistent with the experimentally measured difference in binding free energy *ca*. 1.4 kJ/mol in favour of (*R*)-nicotine. Whereas, the simultaneously applied theoretical model has predicted the difference in the range of 1.6–2.5 kJ/mol. In agreement with experimental observations, the calculated most stable conformation of the substrate–enzyme complex favours the fastest rate of product formation to occur at the 5′-methylene group (Jones et al., 1993; Strickler et al., 2003). A reorientation from this conformation, eventually leading to the formation of the other metabolites (such as 4-(3-pyridyl)-4-oxo-*N*-methybutylamine), would meet an energy penalty related to the binding free energy, therefore higher for (*R*)-nicotine than for (*S*)-nicotine. As a result, in the case of (*R*)-nicotine a significantly lower level of toxic and carcinogenic metabolites is produced. Taking into account the overall cytotoxicity of the compound and its metabolites, it appears that (*R*)-nicotine is approximately eighty times less cytotoxic than (*S*)-nicotine (Yildiz et al., 1998).

Considering, moderate affinity of (*R*)-nicotine to nicotinic acetylcholine receptors combined with substantially lower toxicity, (*R*)-nicotine might be a useful therapeutic agent for neurodegenerative disease and tobacco smoking addiction. (*R*)-nicotine may act through receptor-mediated mechanisms and through non-receptor-mediated mechanisms. Especially, in all cases where (*S*)-nicotine functions through the non-receptor mechanisms (see above), (*R*)-nicotine could be very useful because it would exert less side-effects. For example, both nicotine enantiomers inhibit aggregation of the amyloidal β-peptide and reduce the toxic effects of the peptide on cells (Moore et al., 2004). The (*S*)-nicotine drug delivery systems should also be very easily adopted for (*R*)-nicotine. Therefore, (*R*)-nicotine and perhaps the other minority enantiomers of naturally occurring alkaloids may and should be considered as potential medications if the economical issues connected with their production are overcome. These days, the commercial availability of pure nicotine enantiomers and racemate is limited. For example, the leading providers of laboratory chemicals offer the racemate of nicotine for the price from sixty-five up to two hundreds times higher than that of the natural (*S*)-enantiomer. Since the providers rarely publish details of their production procedures, it seems that the offered (*S*)-nicotine has been extracted from natural tobacco leaves and further purified, whereas the racemate has been obtained *via* the synthetic, yet much more expensive pathway.

Uncommon (*R*)-nicotine can be obtained by two strategies: (i) chemical, enantioselective synthesis of (*R*)-enantiomer and (ii) isolation of (*R*)-nicotine from mixtures of stereoisomers (*e.g.* racemic mixture). Recently, a novel method of synthesis of (*R*)-nicotine has been published (Girard et al., 2000). The proposed synthetic route contains a four-step synthesis of (*R*)-enantiomer starting from commercially available pyridynecarboxyaldehyde, with overall yield 50 to 65%, and of enantiomeric excess *ca.* 92%. Another synthetic route for the synthesis of nicotine with enantiomeric excess higher than 99% by using asymmetric Ir-complex has been described recently (Walter et al., 2005). Both described routes give the uncommon isomer with high enantiomeric excess, but require expensive chemicals of high purity, and therefore are not very economical. The second strategy of obtaining (*R*)-nicotine leads through production of racemic mixture from common (*S*)-isomer (Bownam et al., 1982) or *via* chemical synthesis (Craig, 1933), followed by purification of (*R*)-enantiomer (Armstrong et al., 1998; Aceto et al., 1979; Tang et al., 1998) or possible biodegradation of undesirable (*S*)-enantiomer (Detraglia and Tometsko, 1980; Wackett, 2003). Even though the above synthetic routes leading to (*R*)-nicotine are known, still, there is no inexpensive method of obtaining the uncommon (*R*)-isomer.

6. Concluding remarks

Nicotine has a potential to be widely applied to the pharmacy practice, supporting therapy of some neurodegenerative diseases and neuropsychiatric disorders. Especially, the dextrorotatory enantiomer (*R*)-nicotine as a less toxic alternative should find its own place here. The practically unlimited availability of nicotine from natural resources gives an additional advantage over more selective synthetic nicotinic acetylcholine receptors agonists. Importantly, obtaining nicotine from natural resources does not contradict the economic interest of the tobacco industry, tobacco growers and plantations workers (only in India more than 4.5 million people rely for their livelihood on tobacco production).

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