Nicotine: The Masked Killer

by

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Abbreviation List:

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<th>Abbreviation</th>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
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<td>ROS</td>
<td>Reactive Oxygen Species</td>
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Abstract

Nicotine was first distilled from tobacco sap in 1809. It was first perscripted as medical drug to treat rodent ulcer and constipation. But now it is common knowledge that nicotine does harm to our body. The proper nomenclature for nicotine is \(3-(1\text{-methyl-2-pyrrolidinyl})\text{pyridine}\). It is a levorotatory free base and change between conformation I and II by rotating the pyrrolidine ring. Nicotinic acid (\(\beta\)-pyridine carbonic acid) is obtained by direct oxidation of the base with chromic acid. Nicotine is intaked by cigarette smoking. There are over 4700 chemical compound and radical species formed in cigarette smoke. Smoke contains more than \(10^{18}\) free radicals/g of the tar phase. This paper discusses the chemical metabolism of nicotine and the oxidative stress in cigarette smoking.
Introduction

Nicotine was first distilled from tobacco sap in 1809. Nineteen years later, the main base of tobacco was isolated and separated in pure form from fermented as well as non-fermented tobacco by Posselt and Reimann [1]. They called it nicotine and characterized it as a water-clear liquid, boiling under atmospheric pressure at 246°C, miscible with water, alcohol and ether. Nicotine has the empirical formula C$_{10}$H$_{14}$N$_2$.

Historically, nicotine had been recommended for treatment of numerous symptoms. Jean Nicot, the ambassador of Portugal from 1559 to 1561, planted a strange plant in his garden until it grew abundantly. Then it was heard that a servant of his family had been cured of rodent ulcer on his cheek by applying juice from this plant and bruised herb. From then on this plant became famous. And nicotine was prescribed for use as an enema in treatment of constipation [2]. Currently, nicotine is ingested via cigarettes, smokeless tobacco and chewing gum in social settings.

Two factors favored the rapid spread of tobacco smoking: the simplicity of technique and the quick onset of the effects on the central nervous system, which include stimulation, sedation and a combination of both, depending on the dose and the individual's rate of absorption of the nicotine inhaled.

But the “comfort” feelings cannot cover the deleterious effect of nicotine on the health of the smokers. Nicotine stimulates and subsequently blocks ganglionic cells producing both behavioral stimulation and depression [3]. Nicotine exerts its action indirectly on various organs such as heart and adrenal medulla. In addition, nicotine is metabolized to cotinine, which give rise to potentially harmful N-nitrosamines [4]. This paper focuses on the chemical properties and the metabolism of nicotine.
Chemistry of nicotine

The chemical formula for nicotine is $\text{C}_{10}\text{H}_{14}\text{N}_2$, for a molecular mass of 162.23 kDa. In proper nomenclature, nicotine is $3-(1\text{-methyl-2-pyrrolidinyl})\text{pyridine}$. It is a levorotatory free base [1]. There are four possible confirmations for nicotine, and the most likely configuration of nicotine is a rotation between conformations I and II based on dipole moment calculations of nicotine and nicotine-N-oxide in benzene solutions [5]. It is most stable when the pyridine ring is approximately orthogonal to the pyrrolidine ring. In conformation I, the hydrogen on C3 of the pyrrolidine ring is behind H4 of the pyridine ring while in confirmation II, it is behind H2 of the pyridine ring as seen in Figure 1. Using the quantum mechanical method, Pullman calculated that conformer I is 4 kcal/mole more stable than conformer II. In dilute solutions, however, the preferred conformation is conformer II [1]. In support of this, X-ray analysis of nicotinium salicylate indicates that the N-methyl group of the pyrrolidine ring is trans to the pyridine ring.

Structure of Nicotine

Conformation I

Conformation II

**Figure 1. The structure and the two conformations of nicotine** [5]. Conversion between the two conformations is achieved by rotating the pyrrolidine ring. Nitrogen is indicated by filled circle and carbon is represented by open circle. Hydrogen atoms are not indicated.
Metabolism of nicotine

Direct oxidation of the base with chromic acid yields nicotinic acid (β-pyridine carbonic acid) [6]. Nicotine can be oxidized to N-methyl-nicotine if treated with potassium-ferricyanide and alkali. The oxygen introduced by this method into the pyridine nucleus makes it more sensitive towards chromic acid than the pyrrolidine nucleus. N-methyl-nicotine can then be oxidized to L-hygrinic acid as indicated in Figure 2. From this it was concluded that in nicotine a pyridine nucleus is connected with its β-position α to an N-methyl-pyrrolidine molecule.

![Figure 2. Oxidation of nicotine [6].](image)

Degradation of the natural L-nicotine to L-hygrinic acid proves that the alkaloid possesses the same configuration as L-hygrinic acid, L-stachhydrine and L-proline [2]. The fact that L-proline corresponds in its configuration to L-ornithine shows that hygrinic acid derived from L-nicotine has the configuration of the natural amino acids. This appears to be of importance in considerations with regarding to the biogenesis of nicotine.
Liver has been found to be the major organ to detoxify nicotine [7]. The other tissues in addition to the liver found to metabolize nicotine to a significant extent are the lungs and the kidneys [8]. In all these tissues, the main metabolite is cotinine. Hydroxycotinine is a nicotine metabolite found in liver. The kidney was found to produce $\gamma$-(3-pyridyl)-$\gamma$-oxo-N-methylbutyramide, along with CO$_2$. In lung, no metabolite other than cotinine was found. The metabolism pathway of nicotine is shown in Figure 3.

![Figure 3. Schematic representation of nicotine degradation.](image-url)
Nicotine is present in smoke as an aerosolized liquid. There is approximately 0.5 to 2 mg nicotine per cigarette, depending on tobacco growth conditions and processing. Besides introducing this harmful compound to the bodies of smokers, cigarette smoke can also increase the production of oxidants and induce oxidative stress in smokers.

**Smoking related oxidants**

Cigarette smoke is a complex mixture of over 4700 chemical compounds other than nicotine, including high concentration of free radicals and other oxidants. Cigarette smoke contains free radicals in both the gas and the tar phases [9]. Gas-phase radicals include both inorganic and organic reactive oxygen species (ROS) such as epoxides, peroxides, nitric oxide (\(\cdot\)NO), nitrogen dioxide, peroxynitrite (ONOO\(^{-}\)) and various other free radicals. Gas-phase cigarette smoke contains approximately 10\(^{15}\) radicals per puff, which are primarily of the alkyl, alkoxy, and peroxy type. Nitric oxide (\(\cdot\)NO) is present in cigarette smoke in concentration of 500-1000 ppm, representing one of the greatest exogenous sources of \(\cdot\)NO. It reacts quickly with the superoxide anion (O\(_2\cdot\)) to form peroxynitrite (ONOO\(^{-}\)) and with organic peroxy radicals to give alkyl peroxy radicals (ROONO). In the tar phase, radicals are stable and are predominantly organic, such as semiquinone, which is held in a tarry matrix and can react with oxygen to produce O\(_2\cdot\). Other ROS in the tar phase include the hydroxyl radical (\(\cdot\)OH) and hydrogen peroxide (H\(_2\)O\(_2\)) [10]. Smoke tar contains more than 10\(^{18}\) free radicals per gram. It is also an effective metal chelator and may bind iron to produce tar-semiquinone and tar-Fe\(^{2+}\), which can generate H\(_2\)O\(_2\). Short-lived radicals in the gas phase of cigarette smoke may be quenched immediately in
the epithelial lining fluid (ELF). However, redox reactions in cigarette smoke condensate may produce ROS for a considerable time [10].

**Smoking related oxidative stress**

The oxidative stress increases in smokers and in patients with chronic obstructive pulmonary disease (COPD) as shown in Figure 4. It is known that smoking and chronic bronchitis are both associated with increased numbers of activated neutrophils and macrophages in the airspaces, which release more $\text{O}_2^{\cdot-}$ than those from healthy controls [11]. And a correlation between $\text{O}_2^{\cdot-}$ release by peripheral blood neutrophils and bronchial hyperreactivity in patients with COPD exists, suggesting a role for ROS in the pathogenesis of the airway abnormalities in COPD.

A major site of free radical attack is in polyunsaturated fatty acids in cell membranes producing lipid peroxidation. The end products of lipid peroxidations such as malondialdehyde, ethane and pentane were significantly increased in smokers [12].

![Figure 4](image)

**Figure 4. Detection of free radical from cigarette smoking.** (a) The quinone/hydroquinone radical species detected from the cigarette tar using glass-wool; (b) The EPR signal of the same radical as in (a) using a glass fiber filter; (c) The PBN spin adduct of carbon centered radicals in gas phase of cigarette smoking [11].
Summary

It is common knowledge that smoking is harmful to our body. Each individual cigarette packet is labeled to tell people that smoking is not good. But there are still over one billion smokers all around the world lighting up their cigarettes and enjoying puffing. The major component in tobacco is nicotine. The proper nomenclature for nicotine is \(3-(1\text{-Methyl-2-pyrrolidinyl})\text{pyridine}\). It is a levorotatory free base and can change between conform I and II. Direct oxidation of the base with chromic acid yields nicotinic acid (\(\beta\)-pyridine carbonic acid). Nicotine is mainly intaked by cigarette smoking. Besides this harmful compound, cigarette smoking can also induce oxidative stress inside the bodies of smokers. This is dangerous to smokers because there are over 4700 chemical compound and radical species formed in cigarette smoke. Smoke tar contains more than \(10^{18}\) free radicals per gram. Therefore, nicotine works as a masked killer, making people addict to smoking and doing harms.
Reference


