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Lung Cancer and Nicotine

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Abstract

Nicotine present in smoking and tobacco is major cause of occurrence of lung cancer. The basic nature of nicotine helps in easy absorption through lungs. The binding of nicotine and its derivatives to Nicotinic Acetylcholine Receptor results in significant polymorphic mutations in genes coding the subunits of receptors in various populations like Asian and Caucasians which increases the susceptibility of lung cancer in these populations.

Keywords: Nicotine; Lung cancer; Nicotine acetylcholine receptors

Introduction

Lung cancer is the third most common cancer after prostate gland and breast cancer. A study has been reported 63,000 deaths per year in India due to the lung cancer [1]. Although, there must be numerous of other factors behind the occurrence of lung cancer but most common of all is smoking and tobacco consumption. Thankappan and thresia has reported that there has been 5 million deaths per year i.e., approximately one in ten adults in the world including 2.41 million deaths in developing countries and 2.43 million being attributed to developed countries occur only because of tobacco consumption [2]. Chewing or smoking tobacco and its products contains high amount of carcinogenic nicotine and its derivatives [3]. Excessive inhaling of nicotine results in the alteration of signalling pathways responsible for proliferation, apoptosis and metastasis. Lung cancer culminates from the series of changes in the signalling pathways. One of the changes include desensitization of its cognate receptor Nicotine Acetylcholine Receptor (nAChRs) which is a heterogeneous ligand gated ion channel receptor expressed in numerous cell types and tissues including endothelial cells, gastrointestinal tissue, glia, immune cells, keratinocytes and lung tissue [4]. The nAChRs expressed in lung epithelial cells, are activated by binding of nicotine and additionally NNK leads to opening of ion channels and increase in calcium influx in the cell. Calcium acts as second messenger and activates the cancer signalling pathways along with the secretion of mitogenic factors. This process is considered as hallmark for lung cancer [5]. The single nucleotide polymorphic mutations in the genes coded receptors leads to increase or decrease in susceptibility of lung cancer in different populations.

Nicotine Metabolism and its Receptor

Nicotine is natural occurring clear to pale yellow liquid alkaloid found in plants of Solanaceae family like tobacco plants, tomato plant, and bellanoid plant (Nightshade plant). It constitutes approximately 5% of the dry weight of tobacco and present in various other plants of Solanaceae family in the range of 2–7 μg/kg. According to the IUPAC nomenclature nicotine in named as (S)-3-[1-Methylpyrrolidin-2-yl] pyridine with chemical formula $C_{10}H_{14}N_2$. In its chemical structure nicotine is a bicyclic compound with a pyridine cycle and a pyrrolidine cycle. The nicotine molecule possesses an asymmetric carbon atom and therefore it exists in two enantiomeric forms. In nature, nicotine only exists in the S shape [3]. Fundamentally, nicotine is a weak base and its pKa value is 8.0. At pH 8.0 nicotine gets 50% ionized. This property makes it possible to absorb through skin and mucosal lining of nose, mouth or lungs at basic pH when nicotine is not ionized. Merely in 10 sec nicotine reaches the brain via systematic circulation and binds competitively to the Nicotine Acetylcholine Receptor (nAChRs) present in brain as well as in lungs [6]. Nicotine is get metabolized in liver along with lungs and kidneys and responsible for the production of highly carcinogenic intermediates and by-products which also annex to the Nicotine Acetylcholine Receptor (nAChRs) and cause alterations in the receptors. Metabolism of nicotine produces cotinine and nicotine N-oxide due to oxidation of nicotine by Cytochrome p450 enzymes. Nicotine-1' (5') - iminium ion and 5'-hydroxynicotine are the major carcinogenic intermediates formed during chemical reactions. The nitroso group of nicotine derivatives is culpable for the alkylation of DNA which is very noxious and can give rise to the cancer [6]. The pyrole ring of Nicotine contains a cationic charge which resembles the structure with acetylcholine, a neurotransmitter which binds agonistically to the Nicotine Acetylcholine Receptor (nAChRs) in normal conditions. Structurally, the receptor has five subunits i.e., 2α, β, δ and ε arranged around a central pore. Each subunit is coded by different genes CHRNA, CHRNB, CHRND and CHRNE respectively [7]. Depending on the type of tissues each cell expressed different arrangements of these subunits. Transfection studies have shown that the ratio of α/β subunits in nAChRs subunits depends on the ratio of expression of the encoding nAChR subunit genes. It has been shown that the nAChR α7 in normal human bronchial epithelial cells is up regulated by exposure to nicotine. In mammalian system, there are basically 9α subunits (α1-α7, α9, α10) and 4β subunits (β1-β4) coded by CHRNA1-CHRNA7, CHRNA9, CHRNA10 and CHRNB1-CHNB4 genes located on different chromosomes [8]. The function of these receptors can be altered by the phosphorylation by the activation of second messenger- dependent protein kinases [9]. The signalling mechanism in sensory epithelia and other non- neural cell types are regulated by the nAChRs. In lungs, receptors act as calcium channels which act as secondary messengers in the activation of pathways like PKA, PKC, PI3K/Akt, and MAPK and also linked to the regulatory proteins involve in the regulation of proliferation like src and phosphotidylinositol – 3 –kinase. Nicotine and its derivative bindings on the receptors alter these biological roles of receptors [10].

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Mutations in receptors

The primary cause of lung cancer is mutation in the genes coding numerous enzymes involve in cell cycle regulation and signalling pathways. The mutation in genes of subunits of receptors results in the alteration of signalling pathways [5]. The various studies have been going on to evaluate the synergistic effects genetic polymorphism in nicotine subunits coding genes in occurrence of lung cancer. A single nucleotide polymorphism (SNP) is an alteration in a single nucleotide present in the DNA sequence [11]. The prolonged or repeated exposure to a stimulus often results in decreased responsiveness of that receptor toward a stimulus, termed desensitization. PKA and PKC have been shown to phosphorylate the receptors resulting in desensitization [8]. It has been reported that, after prolonged receptor exposure to agonist, the agonist itself causes an agonist- induced conformational change in the receptor, resulting in desensitization. The long term desensitization of the receptors results in polymorphism of receptor subunits. This polymorphism increases the risk of lung cancer due to disruption in signalling pathways [12]. Polymorphism in genes of encoding α and β- subunits types of receptors effect on gene expression or protein functions. In lung cancer expression of α3, α5 and α7 is predominant. The variations in these receptors are strong candidate of risk factors for nicotine addiction and lung cancer [13]. Multiple genome-wide association studies (GWAS) have implicated the CHRNB4/A3/A5 locus in nicotine dependence and lung cancer [8,12,14].

Discussion

Plethora of studies has been done to observe the polymorphic mutations in receptor coding gene in the different population. Studies have suggested that the α5subunit of nAChRs coded by CHRNA5 gene is predominantly expressed in both NSCLC and SCLC type of lung cancer. This has been postulated that, CHRNA5 may have direct role in lung cancer. Moreover, smokers and non-smokers also expressed different levels of CHRNA5 subunits [15]. Some studies have shown that this polymorphism is not predominant in Asian populations like North Indians, Chinese and Japanese but results contradict with Caucasians which shows high susceptibility towards lung cancer due to presence of mutations in Receptor subunit genes [8,16]. The research has been also done on other genes of subunits of receptor like CHRNA1, CHRNA3, CHRNA7, CHRNA9, CHRNB2, CHRNB4 etc. The results are various among the populations like Caucasians which are found to show more susceptibility towards lung cancer with mutations in these genes but on the other side the Japanese have been shown less susceptible towards lung cancer [9,17]. The studies can be done on Indian populations to find out the role of SNPs in the gene encodes the nicotine acetylene choline receptors subunits towards increase in the lung cancer susceptibility. In future, these studies can be proved to have an important contribution to find out possible reasons of increased susceptibility of lung cancer in different population [18-21].

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