Review Article

An Insight into Cellular and Molecular Changes Associated with Cigarette Smoking: A Review

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ABSTRACT

Cigarette is a mixture of chemicals in which the major component is nicotine. Nicotine results in addiction and its effects are initiated by damaging lipids, activating oxidative sensitive pathways, DNA and other components of the cell. Long-term use of cigarettes causes both stimulatory and inhibitory responses of various cells involved in the secretion of chemokines and cytokines which are known inflammatory markers. In the smoke, particulate phases of cigarettes and smoke consumption causes oxidative/nitrosative stress leads to various diseases. Previous findings from cigarette smoke intake show stimulatory effect by increasing cytokines inside the immune cells and also suppression of immune cells by decreasing the production of cytokines from T-cells which was due to oxidative stress by a generation of ROS and RNS, leads to chronic inflammation. This review provides recent findings from cigarette smoke exposure in experimental animals, mainly smoke-associated free radical-mediated lipids auto-oxidation, nitric oxide-mediated cerebral blood flow, regulation of heme oxygenase, neurokinin (NKR-1) receptors, metalloproteinases (MMPs), and Toll-like receptors (TLRs). These were found to be few targets in the antigen-presenting cells that are involved in invading foreign micro-organisms which are affected by cigarette smoke and they can be a potential target for therapeutic interventions in lung cancer and other tobacco-associated diseases.

Keywords: Cigarette smoking, Reactive Oxygen Species, Oxidative stress, Nitrosative stress, free radicals, Heme oxygenase-1.

INTRODUCTION

Cigarette smoking affects 6 million people worldwide and they suffer from smoking-associated diseases like lung cancer, cardiovascular diseases (CVD), and chronic obstructive pulmonary diseases (COPD). The life span of smokers reduced to 10-15 years compared with non-smokers and develops dementia, stroke, and CVD during their lifetime.[1] According to the American Cancer Society (ACS), smoking causes 20% of cancer and cancer related deaths in the US. In smoking-related cancers, 80% of cases are associated with lung cancer.[2] According to Jha *et al.*, 2008, In India, smoking is killing around 930,000 adults; over 70% of the fatalities will be between the ages of 30 and 69.[3] Tobacco use, in any form, is harmful, and smokeless tobacco use has been linked to a considerable increase in mortality.[4-5] The marketed tobacco products mainly come under two divisions combustible and non-combustible. Cigarettes, cigars, cigarillos, water pipes (hookah), and pipes all come under combustible products. Electronic cigarettes, tobacco used for chewing, snuffing, and dipping were under non-combustible division.[6] Cigarette smoking causes mutagenicity because of the pyrolysis of tobacco products. Also, sister chromatid changes occur due to aldehydes and ketones present in the cigarette. In the early days, it was believed that nicotine is the principal component of cigarette smoke which causes smoke associated issues. But in 1954, it was identified that along with nicotine various polyaromatic hydrocarbons (PAH) were also present in the cigarette.

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From 1954-1980 the major focus was tuned on benzo pyrenes. Some examples of PAHs include naphthalene, phenanthrene, acenaphthene, acenaphthalene, pyrene, and perylene. Other components of smoke include azarenes, low molecular weight phenols, lactones, carbon monoxide, polonium-210, cilastatin, n-nitrosamines, and N-heterocyclic amines.[7] Cigarette smoke destroys the cells which involved in detecting foreign invaders or pathogens such as Epithelial cells, T-cells, Dendritic cells, Macrophages, NK cells, WBC's (Neutrophils), and Phagocytes by the release of free radicals which cause oxidative or nitrosative stress which in turn leads to inflammation. If it persists for a prolonged time, it will result in various disease complications. The cellular and molecular level changes resulted as a consequence of free radicals released from cigarette smoke. This review is initiated because there is a criticism in the cellular molecular events related to cigarette smoke associated inflation like free radicals released from cigarette smoking cause damage to cells by both stimulatory and inhibitory action by oxidative or nitrosative stress which increases and decreases the levels of cytokines and chemokines causes chronic inflammation and various other disease complications like auto-immune disorders, cancer, CVD, COPD, and diabetes. So, this review covers all the literature related to cellular and molecular events associated with cigarette smoke, so there will be a clear picture of molecular events which lead to cigarette smoke-associated complications and the researcher can easily pick up the markers which are least explored. The study's main goals are to discover about cigarette smoke-induced cellular and molecular alterations and proposes novel prospective targets for cigarette smoke-related clinical symptoms that have yet to be investigated.

FREE RADICALS

Free radicals are unstable molecules that can be formed both endogenously and exogenously. Endogenously formed free radicals during normal cellular metabolism and have biological effects such as initiating immune response for fighting pathogens, cellular signalling by increasing cGMP levels,[8] mitogen respiration[9] and redox regulation.[10] The exogenous free radical formation is caused by exposure to harmful or environmental stimuli such as alcohol, cigarette smoking, contaminants, and other toxic chemicals which cause oxidative and nitrosative stress, DNA, lipid, and protein damage and can lead to pathological conditions such as Diabetes Mellitus, Respiratory disorders, Cancer, Cardiovascular diseases, Atherosclerosis and Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Multiple sclerosis, Cataracts and Aging.

Types of Free Radicals

The major free radical types are ROS, RNS, and non-radicals. ROS radicals are mainly superoxide anion, hydroxyl, alkoxyl, and peroxyl radicals. RNS radical's examples are nitric oxide, nitrogen dioxide and RNS non-radicals are peroxy nitrites, nitrosyl cation, nitrosyl anion, dinitrogen trioxide, dinitrogen tetra oxide, nitrous acid, peroxy nitrous acid, and nitryl chloride.[11] Non-radicals are not unpaired electron free radicals; rather, they include, contribute to, or are converted into free radicals. The oxygen-derived free radical is the most critical among them (O_2).Other examples are hydrogen peroxide, singlet oxygen, ozone, organic peroxide, hypochlorous acid, and hypobromous acid.[12] The most important ROS radicals were superoxide, hydroxyl, and alkoxyl radicals were the products of lipid peroxidation, protein carbonyls upon protein oxidation and ROS non-radical such as hydrogen peroxide and singlet oxygen contribute to the development of the diseased condition. The RNS radical and non-radical are nitric oxide and peroxy-nitrite causes DNA damage by breaking its double-strand[13] which further undergoes deamination, inflammation, the proliferation of cancer cells and finally, no programmed cell death which further increases the levels of free and non-radicals.[14-15]

Sources of Free Radicals

Mitochondria contribute to the major production of ROS through the Q cycle in which the electron transport chain complex 1 and 2 transfers electrons with the help of its NADH dehydrogenase and cytochrome C reductase. Now, the transferred electrons form QH2 and further coenzyme Q rebirth takes place through the semiquinone anion (Q.-). Semiquinone anion releases an electron to oxygen and forms a superoxide anion. SOD reacts further with superoxide anion to form H_2O_2 and catalases H_2O_2 to water. The peroxisome is the next contributor of ROS wherein the oxygen accepts an electron to form hydrogen peroxide with the help of enzymes involved in β-oxidation of fatty acids such as acyl Co-a oxidases, d-amino oxidase, urate oxidase, xanthine oxidase, d-aspartate oxidase, L-α hydroxyl oxidase. Alterations in the levels of enzymes cause an imbalance in the generation of free radicals. Endoplasmic reticulum generates free radicals with the help of cytochrome p-450, b5, and diamine oxidase, and also the other enzymes contribute thiol oxidase transfer electron from thiol protein to oxygen to form H_2O_2. Some of the other contributors for oxidative/nitrosative

stress are xanthine oxidase, inflammation, phagocytosis, arachidonate pathways, exercise, ischemia/reperfusion injury, and some external triggers for free radicals are cigarette smoke, environmental pollutants, radiation, certain drugs, pesticides, industrial solvents and ozone.[16]

Cigarette Smoke

Cigarette smoke particles (gas phase) are highly concentrated consist of a mixture of many compounds that occurs from distillation, pyrolysis, and combustion of tobacco. The particle size of smoke varies according to its usage, wherein the gas phase particles are those formed after lighting a cigarette, and the particulate phase is the matter present in the filter. Usually, smoke formation occurs in 2 phases; direct lighting of cigarette and inhalation of smoke called mainstream smoking and smoke intake in between the puffs called smouldering or side stream smoking. The amount of puffing increases with decreased smouldering in mainstream smoking and decreased puffing with increased smouldering in side stream smoking.[17] Studies indicate that compared with mainstream smoke collected under standard smoking parameters, side stream smoke has higher levels of PAHs, nitrosamines, azoarenes, aromatic amines, carbon monoxide (CO), nicotine, ammonia, pyridine,3-butadiene, acrolein, isoprene, benzene, and toluene.[18] When puffing increases the toxicants from the side stream smoking decreases. The tobacco burn in side stream smoking falls to 400°C from 900°C in mainstream puffing. Moreover, cyanide was found to be one of the major components of mainstream smoking along with compounds like catechol and hydroquinone.[19] In the case of side stream smoke compounds like phenol, cresol, guaiacol, formic acid, and acetic acid levels were high.[20]

FREE RADICALS AND CIGARETTE SMOKING

Free radicals generation upon cigarette consumption mainly occurs in two different phases, the first phase is tar phase (TP)/aqueous cigarette tar (ACT) in which the oxygen is reduced to superoxide ion and hydrogen peroxide and finally to hydroxyl radical called ROS through Quinone-hydroquinone-semiquinone system resulted in the depletion of radicals such as quinone/hydroquinone.[21] The second phase is the smoke phase (SP) where reactive RNS were generated through oxidation of nitric oxide (NO) to nitrous oxide (NO_2), RNS further reacts with one of the major components of smoke isoprene to increase the free radical's level. This oxidative/nitrosative stress[22] causes the inactivation of alpha1-proteinase inhibitor[23] present in the macrophages and neutrophils, affects the protease-antiprotease balance[24] The important biological molecules and biomarkers found upon free radical generation were identified such as 8-hydroxydeoxyguanosine (8-OHdG) for DNA damage, 9-prostane for lipid peroxidation, and change in oxidized: reduced glutathione (GSSH: GSH) ratio[25] for enzyme inactivation and ultimately the free radicals adversely affect the major biomolecules causes changes in their redox potential. The smoke phase (SP) free radicals were the major or primary free radicals formed first when there is smoke decomposition. This causes the initiation of the radicals to form oxygen free radicals and oxidative stress. The formation of secondary radicals due to the long-term smoke consumption takes place and seems to have a major impact on health because of its synergistic action. These secondary radicals were termed as tar phase (TP) free radicals contains hydroquinone and catechol. The amount of secondary oxygen free radicals present in the body upon chronic smoking is greater than that of primary free radicals.[26]

EXISTING/CURRENT KNOWLEDGE ON CIGARETTE SMOKING

Cigarette smoking exerts inflammatory and suppressive effects on immune cells where the free radicals generated in the gas phase damage the upper airway and semiquinone radicals in the particulate phase led to oxidative stress and nitrosative stress. Epithelial cells were further damaged upon oxidative stress by lipid peroxidation, activation of oxidative sensitive pathways, and DNA damage which in turn activates intracellular cascade leads to the production of IL-8 and TNF-α, inflammatory mediators cause chronic inflammation. The suppressive effect by inhibiting T lymphocytes-1 cell response and activates T lymphocytes 2 cell causes a decrease in IL-12 and IL-23 from Th-17. These effects were studied in dendritic cells especially lung dendritic cells. Cigarette smoking affects mucosal immunity by interacting with TLR-3 receptors helps in the recognition of pathogens, present in epithelial cells which increase the production of chemokines through the activation of AP-1 and NFκβ which in turn cause altered corticosteroid resistance and altered cell death regulation.[27] The other pathways are MAPK, STAT activation from cigarette smoke exposure. Upregulation of anti-apoptotic factors causes activation of NFκβ. Activation of Ras for the stimulation of RAGE receptors takes place from cigarette smoke consumption. The ROS generated activates the AP-1 pathway for the production of IL-8. The types of pathway activation take place in dendritic cells which also leads to the production of PEG-2, IL-8,

and IL-10.[28] Accumulation of macrophages occurs in the lungs, which is functionally impaired and reduced phagocytic uptake of bacteria and apoptotic cells leads to impaired wound healing accumulation of apoptotic and inflammatory cellular debris. The macrophage in turn produces TNF-α. Natural Killer cells are also damaged from cigarette smoke exposure which in turn decreases the IFNγ and TNFα synthesis. Smoking-associated microRNA's were found to be associated with the inflammatory process and also with organ damage.[29] A highly sensitive C reactive protein (hsCRP), carotid intima-media thickness, and ankle-brachial index were found to be expressed high in current smokers when compared with the non-smokers.[30] The cohort study from patients who smoke increases the level of CRP, Fibrinogen, IL-6, and CEA levels compared with non-smokers and also IL-8 and several other cytokines and chemokines were secreted, elevated levels of PGE-2 were found. The RBCs, haematocrits, haemoglobin, MCV, MCH, MCHC, Pct, and RDW levels were higher in smokers compared to non-smokers.[31]

RECENT FINDINGS ON CIGARETTE SMOKING

Lipid Peroxidation and Mitochondria Dysfunction

A free-radical mediated chain of reaction causes lipid auto-oxidation which means the unsaturated lipid bilayer reacts chemically with free radicals to generate primary or secondary lipid peroxidation products.[32] The free radicals formation upon cigarette smoke exposure on experimental rats causes an increase in Na^+, Ca^+ ions inside the cell and K^+, Mg^+ outside the cell leads to altered activity of membrane-bound enzymes such as Na^+/K^+ exchanger, Ca^+ ATPases and Mg^+ ATPases[33] indicates the disturbance in the generation of an action potential in neuron causes ionic equilibrium imbalance and leads to altered cell signalling, protein, DNA damage, and cytotoxicity.[34] Moreover, increased levels of lipid peroxides, lipids, total cholesterol, triglycerides, phospholipids, C/P-cholesterol/phospholipid ratio and mitochondrial enzymes such as isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, succinate dehydrogenase, malate dehydrogenase, NADH dehydrogenase, and cytochrome C oxidase and also oxidative phosphorylation measured variables (O/ADP ratio, ATP quantity, rate succinate oxidation) were altered leads to no electron transport chain reaction and decrease concentration gradient leads to decrease ATP synthesis and mitochondrial dysfunction[35] An increase in the levels of carbonyl which was found to be the secondary free radicals product contributes to lipid peroxidation and elevated levels of cytochrome p450,

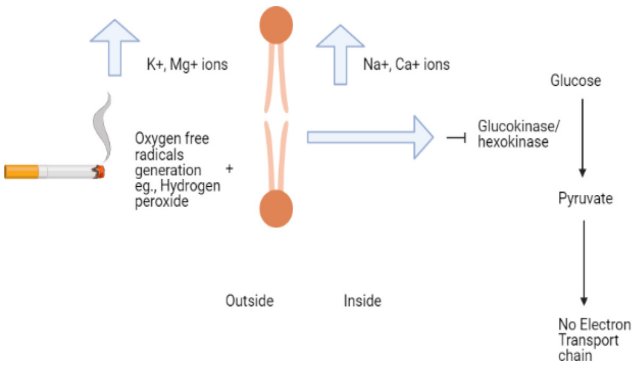

Figure 1: Effect of cigarette smoking in the lipid-containing cell membrane.

NADPH oxidase, xanthine oxidase were found. Now, it is clear that cigarette smoking alters the unsaturated lipid bilayer and disturbs neuronal conduction by disturbing the ion channels present in the glial cell. It also interacts directly or indirectly (through the cell membrane) with the glucose metabolism inside the cell, inhibits the formation of two molecules of pyruvic acid which enters the mitochondria for the electron transport chain and generation of ATP molecules. Because of impaired glycolysis, no sufficient pyruvate molecules enter into mitochondria for the TCA cycle, for the synthesis of lipids, proteins, nucleic acids, and also long-term use of cigarette causes decrease glycogenesis, glycogenolysis, gluconeogenesis which are the part of glucose metabolism. (Figure 1)

Free radicals from the cigarette smoke increase the levels of Na^+, Ca^+ ions inside the cell and K^+, Mg^+ ions outside the cell, hypothesized to alterations in enzymes involved in glucose metabolism and electron transport chain is inhibited.

Endogenous Antioxidants Levels

Anti-oxidants defence system (both enzymatic and non-enzymatic) inactivation takes place when cigarette smoke was exposed in rats, found the accumulation of Cu, Fe, and loss of ceruloplasmin activity, Zn and Se. Also, the decrease in anti-oxidants enzymes such as SOD, Catalase, Glutathione Peroxidase(GPx), Glutathione reductase(GR),[36] monoamine oxidase takes place.[37] The reaction of free radicals and unsaturated lipid layer causes lipid autoxidation upon cigarette smoke exposure, resulting in the release of creatine kinase isoforms (CK-MM, MB,BB) found in the brain into the blood which was quantitatively measured.[38] Also, lactate dehydrogenase (LDH) was found to disperse into the systemic circulation and there will be low levels in the brain, this was due to the lipid-associated with free radicals release.[39]

Nitric oxide-mediated Cerebral Blood Flow

Cigarette smoke extract (CSE) causes nitric oxide synthase inhibition. Results in decreased nitric oxide synthesis from the endothelial cells and causes vasoconstriction and decreases cerebral blood flow.[40] Nitric oxide levels in the rats were low when they were exposed to nicotine and cigarette smoke and cause constriction of blood vessels.[41] e-NOS protein expression in mice.[42] Cigarette smoking in rats exhibits a decrease in glucose supply and blood flow in the cerebral vasculature, this is due to a decrease in the synthesis of nitric oxide from the endothelial cells and nitrergic nerves of vascular smooth muscle. Nitric oxide is a hormone and potent vasodilator released during cholinergic neuron stimulation, bradykinin release, substance P activation, and shear stress. Upon the release of acetylcholine (Ach) and synthesis of nitric oxide happens results in cerebral vessels receive enough blood for dilation. Consumption of cigarette smoke increases nicotine content in the system, tends to release free radicals which react with i-NOS proteins to inhibit the synthesis of Nitric oxide which decreases blood flow and causes cognitive abnormalities.[43] Decrease blood flow causes cerebral hypoperfusion and cognitive abnormalities lead to Alzheimer's disease. The reduced blood flow increases amyloid-beta deposition in the brain and decreases the clearance of amyloid-beta. Amyloid-beta deposition in turn inhibits endothelial function and the vicious cycle was repeated due to the release of free radicals upon cigarette smoking. Endothelial cells and cholinergic neurons release NO upon stimulus, which in turn causes vasodilation and increases cerebral blood flow. (Figure 2)

Heme oxygenase-1

Heme oxygenase is an endogenous cytoprotective agent and also an antioxidant found in the endothelial cells of blood vessels. Rats exposed to cigarette smoke and human umbilical vein endothelial cells (HUVEC) cultured with cigarette smoke cause increases ROS levels and subsequently decrease the expression of heme-oxygenase.[44] Fibroblasts exposed to cigarette smoke extract (CSE) increases the expression of heme-oxygenase HO-1 but not HO-2 and reduces the levels of glutathione (GSH).[45] Cigarette smoking was found to reduce the levels of heme oxygenase-1 by inhibiting the heme oxygenase gene expression which was regulated by the Nrf-2 regulator. Heme oxygenase-1 is a Heat shock protein (HSP-32) found in endothelial cells essential during the process of protein formation to 3D structure, is one of the isoforms involved in a rate-limiting step during catabolism of heme, which form biliverdin and reduced to bilirubin with the help of bilirubin reductase found to be an anti-oxidant, to inhibit the Reactive oxygen species, Inflammation, Apoptosis. Heat Shock Protein (HSP-70) abnormalities were also found upon smoke exposure in rats.[46] Therefore, Cigarette smoking causes an increase in ROS levels which decreases the expression of Heme oxygenase induces neuronal and physiological changes.

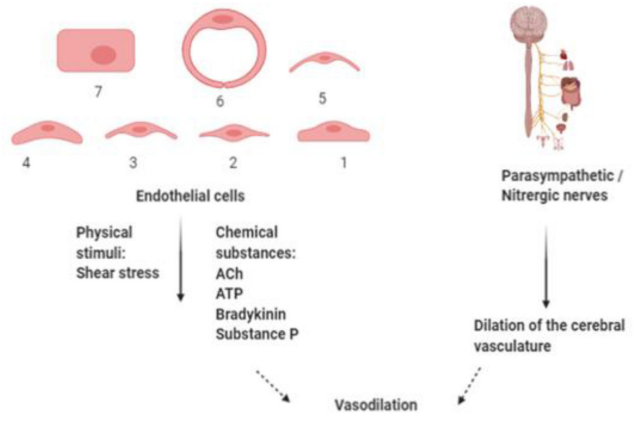

Figure 2: Nitric oxide synthesis impairment associated with Cigarette smoking.

Effects of cigarette smoke and nicotine in NK-1 receptors

Environmental Tobacco Smoke (ETS), side stream exposure in mice causes an increase in the levels of Substance P subsequently there was a higher neurokinin-1 receptors (NKr's-1) expression causes increased inflammation.[47] Cigarette smoke exposure in tachykinin NK-1 receptor knock-out mice causes sedimentation of inflammatory cells like macrophages and dendritic cells and causes an increase in the levels of MIP-3α/CCL20, IL-8, and TNF-β. The study indicates Cigarette smoke exposure causes the NK- receptors upregulation and sensitization due to increased levels of substance P[48] production and results in increased inflammation. Prenatal nicotine exposure in rats causes an increase in the levels of substance P in the brain stem and pre protochykinin-A mRNA levels in the new-born pups in carotid bodies and the petrosal ganglia.[49] Moreover, cigarette smoke condensate in macrophages increases the activation of NK-1 receptors and increases nuclear factor kappa B levels. This shows increased inflammation by the accumulation of pro-inflammatory cytokines.[50] Macrophages with lipopolysaccharide (LPS) and Cigarette smoke condensate exposure activate the Nuclear factor-kappa B and substance P levels by increasing expression of neurokinin-1 receptors especially by elevated levels of IL-1s and TNF-α.[51] Also, various studies reported that there is a decrease in

glomus cells, mRNA levels of NK-1 receptors, NFκβ, immunoreactivity of tyrosine hydroxylase in the carotid body upon prenatal nicotine exposure (PNE).[52]

Substance P

Substance P (SP) is an undecapeptide that derives from alpha, beta, and gamma pre-tachykinin gene transcripts. SP contains 11-amino acid hypotensive peptide, where they are present in a wide variety of cells in the gastrointestinal tract, spinal cord, and brain.[53] It is secreted by nerves and inflammatory cells such as macrophages, eosinophils, lymphocytes, and dendritic cells and acts by binding to the neurokinin-1 receptor (NK-1R).[54] SP was found to be secreted along with other peptides/neurotransmitters from the neurons acts as a neurotransmitter and neuromodulator. In the periphery, they act as a neurotransmitter and send sensory information to the brain, and the release of SP in the periphery causes vasodilation and increased vascular permeability and leads to neurogenic inflammation. SP, positive fibre cells, was found to be in the hindbrain reticular nuclei than in adjacent nuclei along with epinephrine and norepinephrine.[55]

Neurokinin-1 receptor

It comes under the tachykinin family of receptors; it is present in the vomiting centre (nucleus tractus solitaries and postrema) of the brain involved in the neurotransmission and inflammatory process. NK-1R has a greater affinity towards SP than other members of the family NKR-2, NKR-3. These receptors were found in the nervous and immune systems and have a wide variety of biological responses such as pain transmission, vasodilation, endocrine, paracrine secretions, modulation of cell proliferation, neuromodulation, sensory neuronal transmission in stress, depression, emesis, and anxiety.

G-protein coupled action

Upon activation of NKR-1 by substance P, G-protein coupled Gs type activation causes α subunit to activate adenylyl cyclase, cAMP, and protein kinases, and finally, NFKβ nuclear factor kappa B causes negative activation. Gi type activation of both α, βα subunits causes activation of Src protein and involved in DNA synthesis, anti-apoptotic, cell proliferation. B, γ subunits of Gs and Gq type of G-protein receptors activates PI3/Akt signalling pathway by Phospholipase activation causes IP3 and DAG synthesis which in turn causes the release of calcium ions from endoplasmic reticulum for DNA synthesis, anti-apoptotic, cell proliferation. Gq type activation α subunit activates phospholipase C and increases in Ca activates protein kinase and activates a cascade of kinase protein Shc protein Erk1/2 pathway, whereas, βγ subunits stimulate β arrestin and Src, Shc protein activation for Erk1/2 stimulation, helps in the synthesis of pro-inflammatory cytokines IL-1,IL-8, and cell proliferation.[56] Cigarette smoking causes an increase in levels of SP expression of neurokinin receptors leads the cell to altered proliferation, cell inflammation by increasing cytokine levels, reduced DNA synthesis, decrease in the levels of calcium, and finally to apoptosis.[57]

Tissue Inhibitor of Metalloproteinase (TIMPs)

Moreover, the level of metalloproteinase was estimated in the walls of cerebral arteries in experimental animals. MMP-2, MMP-9 levels were estimated upon smoking in animals and found to have an increase in MMP-9 and its distribution. MMP-2 was found to be precipitated upon smoke exposure.[58] Tissue Inhibitors of metalloproteinase (TIMPs) are the membrane-bound proteins helpful in counteracting the depletion of extracellular matrix (ECM) by metalloproteinases. TIMPs family members are TIMP-1, TIMP-2, TIMP-3, TIMP-4 which are secreted by fibroblasts exhibit homeostasis to maintain the function of growth factor, that is the levels of TIMPs and MMPs should be balanced or it leads to excessive ECM loss or ECM accumulation. So, TIMPs are essential in MMPs growth factor regulation and inhibition.[59]

Matrix Metalloproteinase (MMPs)

Matrix metalloproteinases the Zn+ dependent protein family MMP-2 and MMP-9 release from matrix metalloproteinase degrade the extracellular matrix (ECM). Therefore, TIMPs are the proteins that have N terminal shows inhibitory action upon binding to metalloproteinases, and C terminal has non-inhibitory action upon binding to pro-MMP-2 and pro MMP-9 zymogens.[60]

MMPs and Inflammation

Macrophages, granulocyte, leukocyte[61] are the few cells release MMPs for the balance or homeostasis to TIMPs. Now upon cigarette smoking, the levels of MMPs-9 and MMPs-2 were found to be high or precipitation in cerebral arteries of rats. This may be due to increase production of MMPs from its matrix upon cigarette smoking alters the levels of TIMPs inhibits the homeostasis by loss of ECF and inhibition of growth regulators in brain microglial cells.[62] This, in turn, affects the metabolism of dead neurons and the immunity process in the brains of the rat.

Toll-like Receptors (TLRs)

Patients with COPD were analysed for any inflammation, which indicates that TLR4 and TLR9 expression from immunostaining of lung tissue.[63] Cigarette smoke increases CXCL8 production from neutrophils by activating TLR9 receptors.[64] CSE suppresses TNFα, IL-8, IL-10 and reduces innate immune response by increasing the production of CXCL8 from TLRs in macrophages.[65] TLRs function such as TNFα, IL-6, and IL-1β production is suppressed once treated with CSE and also inactivation of NF-Kb and activation of histone acetylase in macrophages was seen.[66] Pathogen-associated molecular patterns, microbial sensing proteins, and other certain molecules were detected by TLRs by pattern recognition either by innate or adaptive immunity. Firstly, the cells which contain TLRs detect foreign invaders and counteract the harmful effects by providing innate immunity, if the immune response is more than normal it may affect the surrounding healthy tissues also. Thereafter, adaptive immunity response takes place with the help of B-cells and T-cells, this may take quite long. TLRs 1, 2, 4, 5, 6 recognize the pathogens in the plasma membrane whereas; TLRs 3, 7, 8, 9 detect the invaders in single-stranded RNA or DNA of the cell. There were also damage-associated molecular patterns that alter the body to cell or tissue injury, wherein the release of intracellular components, extracellular components upon cell injury, and necrosis cause activation of TLRs. TLRs are found in mast cells, macrophages, and dendritic cells. Upon activation of TLRs, there was a set of ten protein kinases activation called signal transduction which activates specifically ILAKs IL-1R associated protein and MAPKs for the transcription of proteins such as cytokines and immune response.

Cigarette Smoking and Neurotransmitter Levels

Cigarette smoking was found to increase the levels of acetylcholinesterase activity.[67] Cigarette smoking impairs excitatory neurotransmitters such as epinephrine, norepinephrine, serotonin, dopamine, glutamate, and inhibitory neurotransmitters like acetylcholine, GABA. They also found to inhibit the enzyme monoamine oxidase which is responsible for the catabolism of excitatory neurotransmitters such as epinephrine, norepinephrine, and dopamine.[68] The electronic cigarette was used to study nicotine addiction and found to have low levels of dopamine in the striatum and increased glutamate in striatum and glutamine in both striatum and frontal cortex decreased levels of GABA in the striatum. Therefore, the neurotransmitter exocytosis was found to be impaired upon smoke exposure.

Cigarette Smoking in Prenatal Rats

Prenatal rats were used to study the harmful effects of cigarette smoking in pups during pregnancy. Smoking in pregnancy was found to harm neonatal brain development and progression continues, so it is essential to study the effects of smoke in pregnant experimental animals. Smoking in pregnant rats resulted in slight alterations of physical reflexes like eyelid reflex and ear unfolding, neural maturity like hind limb grasping, forelimb grasping reflexes. Therefore, cigarette smoking during pregnancy was found to alter the normal growth of neurons and brain development.[69] During perinatal period, rats which are exposed to smoke has increased butyryl cholinesterase activity. This may result in increase in psychotic symptoms during adulthood.[70] According to Yosouf Mohsenzadeh *et al.*, study exposing pregnant rats to nicotine leads to increase in inflammatory markers like IL-6 and TNF-α.[71]

CONCLUSION

The existing findings from the literature search shows cigarette smoking increases release of free radicals and result in oxidative and nitrosative stress in the antigen-presenting cells. This leads to an inflammatory response by increasing the production of IL-8 and TNF-α (inflammatory mediators) which causes chronic inflammation and suppressing effect by inhibiting Th-1 response, subsequently Th-2 response increases cause low IL-12, IL-23 production. Now, it is clear from existing evidence that cigarette smoking, not all ways show inflammatory activity but also the suppress the cells fighting against pathogens. Upon free radical-mediated activation, there is an activation of pathways like NFκB, AP-1, STAT, and MAPK which increases or decreases the levels of chemokines and cytokines. Finally, altered cell death regulation, altered chemokine secretion resistance, upregulation of anti-apoptotic factors (NFκB), Ras's activation for RAGE receptors functioning for advanced aging in epithelial cells, AP-1 activation from ROS in macrophages, and monocytes for IL-8 production causes corticosteroid resistance inflammation. Therefore, cigarette smoking affects chronic inflammation in the airways as well as simultaneously modulating mucosal function.

The major targets which get effected in cigarette smoke are 1. Ionic equilibrium in the cell and energy generation from mitochondria get altered. These further effects glucose metabolism and result in hyperglycaemic conditions 2. Smoke causes nitric oxide associated vasoconstriction and decreases the amount of blood flow. Constriction of blood vessels also causes major

disease like Alzheimer's dementia by increasing the amyloid-beta deposition which in turn activated Tau protein damages the neurons and decreases the size of the brain in Alzheimer's patients. By inhibiting the enzymes i-NOS, e-NOS involved in the production of nitric oxide provide insight to reduce the levels of APP and Tau in Alzheimer's and other tobacco-associated NO-mediated diseases. 3. Anti-oxidant, heme oxygenase (HO-1) was found to be mainly affected by cigarette smoking, therapeutic approaches by increasing the level of heme oxygenase (HO-1) for tobacco-associated diseases. 4. Neurokinin receptors (NKR-1) activation directly from the cigarette smoke as well as from the substance P release from antigen-presenting cells associated with cigarette smoking was evident. Now, the competitive inhibitors for substance P activation of NKR-1 can be one therapeutic approach, another is directly by inhibiting the neurokinin receptors. This can be done by activating the GPCR's. 5. TLRs activation from cigarette smoking in pathogen detecting cells was seen observed, which increases the levels of chemokine and cytokines and decreases TNFα. This provides insights for COPD where the smoke-induced TLRs inhibition can be a therapeutic approach for the reduction of inflammation in lung cancer and COPD patients. Therefore, the targets mentioned above, in brief, provide a therapeutic approach to discover new ligands which decrease their specific expression. The approach can be 1. directly inhibiting or activating the receptor or proteins 2. Altering the inflammatory mediators' production from the activation of these primary targets 3. Altering the expression of genes which increases the production of chemokines and cytokines 4. By inhibiting the pathways which were activated by cigarette smoke.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ROS: Reactive oxygen species; **RNS:** Reactive Nitrogen species; **COPD:** Chronic Obstructive Pulmonary Disease; **CVD:** Cardiovascular diseases; **NO:** nitric oxide; **MMPs:** matrix metalloproteinases; **NKR:** Neurokinin receptors; **TLRs:** Toll-like receptors; **PAHs:** Polyaromatic hydrocarbons; **NK:** Natural Killer; **SOD:** Superoxide dismutase; Q-cycle: Quinone cycle; **NADH:** Nicotinamide adenine dinucleotide; **TP:** Tar phase; **SP:** Smoke phase; **ILs:** Interleukins; **TNF:** Tumour Necrosis Factor; **Th:** T-cells; **AP:** Activator protein; **NFκB:** Nuclear Factor kappa B; **STAT:** signal transducer activator; **PGEs:** Prostaglandins; **hsCRP:** high sensitive C reactive protein; **e-NOS:** endothelial nitric oxide synthase; **HO-1:** heme oxygenase; **SP:** substance P; **ECM:** extracellular matrix; **TIMPS:** Tissue inhibitor of metalloproteinase; **HSP:** Heat shock protein**; TCA:** Tricarboxylic acid; **cGMP:** cyclic adenosine monophosphate; **CEA:** carcinoembryonic antigen; **MCV:** mean corpuscular volume; **MCHC:** mean corpuscular haemoglobin concentration; **Pct:** Procalcitonin; **RDW:** Red cell distribution width.

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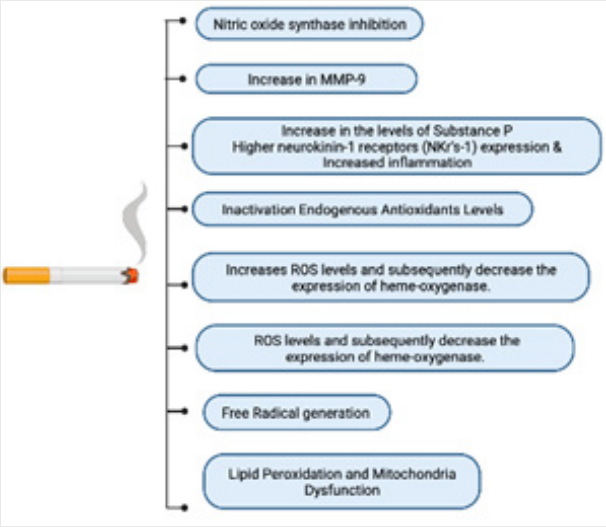
PICTORIAL ABSTRACT



SUMMARY

It is clear from existing evidence that cigarette smoking, not all ways show inflammatory activity but also the suppress the cells fighting against pathogens. Upon free radical-mediated activation, there is an activation of pathways like NFκB, AP-1, STAT, and MAPK which increases or decreases the levels of chemokines and cytokines. Finally, altered cell death regulation, altered chemokine secretion resistance, upregulation of anti- apoptotic factors (NFκB), Ras's activation for RAGE receptors functioning for advanced aging in epithelial cells, AP-1 activation from ROS in macrophages, and monocytes for IL-8 production causes corticosteroid resistance inflammation. Therefore, cigarette smoking affects chronic inflammation in the airways as well as simultaneously modulating mucosal function. This review provides recent findings from cigarette smoke exposure in experimental animals, mainly smoke-associated free radical-mediated lipids auto-oxidation, nitric oxide-mediated cerebral blood flow, regulation of heme oxygenase, neurokinin (NKR-1) receptors, metalloproteinases (MMPs), and Toll-like receptors (TLRs). These were found to be few targets in the antigen-presenting cells that are involved in invading foreign micro-organisms which are affected by cigarette smoke and they can be a potential target for therapeutic interventions in lung cancer and other tobacco-associated diseases.

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