Review Article

Indian J Med Res 142, September 2015, pp 245-260
DOI:10.4103/0971-5916.166529

Role of oxidative stress & transient receptor potential in chronic obstructive pulmonary disease

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Received October 4, 2013

Chronic obstructive pulmonary disease (COPD) affect millions of people worldwide and is known to be one of the leading causes of death. The highly sensitive airways protect themselves from irritants by cough and sneeze which propel endogenous and exogenous substances to minimize airway noxious effects. One noxious effect of these substances is activation of peripheral sensory nerve endings of nociceptor neurons innervating these airways lining thus transmitting dangerous signals from the environment to the central nervous system (CNS). Nociceptor neurons include transient receptor potential (TRP) ion channels, especially the vanilloid and ankyrin subfamilies, TRPV1/A1 which can be activated by noxious chemical challenges in models of airways disease. As oxidative stress may activate airways sensory neurons and contribute to COPD exacerbations we sought to review the role that TRP channel activation by oxidative signals may have on airway responses. It would be prudent to target the TRP channels with antagonists and lower systemic oxidative stress with agents that can modulate TRP expression and boost the endogenous levels of antioxidants for treatment and management of COPD.

Key words COPD - hyperresponsiveness - oxidative stress - ROS - transient receptor potential

Introduction

Chronic obstructive pulmonary disease (COPD) is a multi-factorial disorder affecting millions of people worldwide and is currently the fourth leading cause of death[1]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a disease state associated with progressive airflow obstruction that is not fully reversible[2], and is closely tied to oxidative damage of cell. Increase in prevalence of COPD is not well understood in India as the important variables such as smoking, domestic smoke exposure, and outdoor pollution, socio-economic status and ethnicity are ill-defined[3]. Pena and co-workers[4] reported prevalence ranging 5-18 per cent in seven regions of Spain. The 2005 Latin American Project[5] for the Investigation of Obstructive Lung Disease (PLATINO) study reported prevalence ranging 8-20 per cent in five Latin American cities. Caballero and coworkers[6] found prevalence of GOLD stage I COPD ranging 6-13 per cent in Colombia and the international Burden of Obstructive Lung Disease (BOLD) study identified prevalence in males ranging from 11 per cent in China

to 24 per cent in South Africa[7]. Overall, the evidence suggests substantial geographical variations in COPD prevalence that remain largely unexplained[7]. COPD is not only confined to the lungs but is being recognized as a systemic disease with multisystem manifestations. In a sub-continent like India, there is a need to understand different phenotypes in relation to clinical presentation, spirometric parameters, exacerbations and finally prognosis[3]. In a multicentric study of Indian population on smoking and associated respiratory morbidities leading to the development of COPD/other respiratory disorders, it has been emphasized that benefits of quitting smoking need to be taken on a priority basis[8,9]. Apart from the exogenously produced oxidants, the body is also exposed to endogenously produced reactive oxygen species (ROS). These are quenched, to an extent by the antioxidant enzymes such as glutathione-S-transferase (GST) and superoxide dismutase (SOD) to maintain redox homeostasis. Oxidative stress generated due to cigarette smoke/environmental pollutants is known to irritate epithelial cells of the lungs and various cells related to immune response. This leads to an imbalance in redox homeostasis and causes deleterious damage to cell components (Fig. 1), resulting in COPD condtion[10].

Chemical airway exposures are detected by the olfactory, gustatory, and nociceptive sensory systems that initiate protective physiological and behavioural responses. Using physiological, imaging, and genetic approaches, the transient receptor potential (TRP) ion channels in sensory neurons were shown to respond to a wide range of noxious chemical stimuli, initiating pain, respiratory depression, cough, glandular secretions, and other protective responses. The reactive chemicals are detected by the peripheral sensory neurons by activating TRPV (vallinoid), TRPA1 (ankyrin), or ASIC

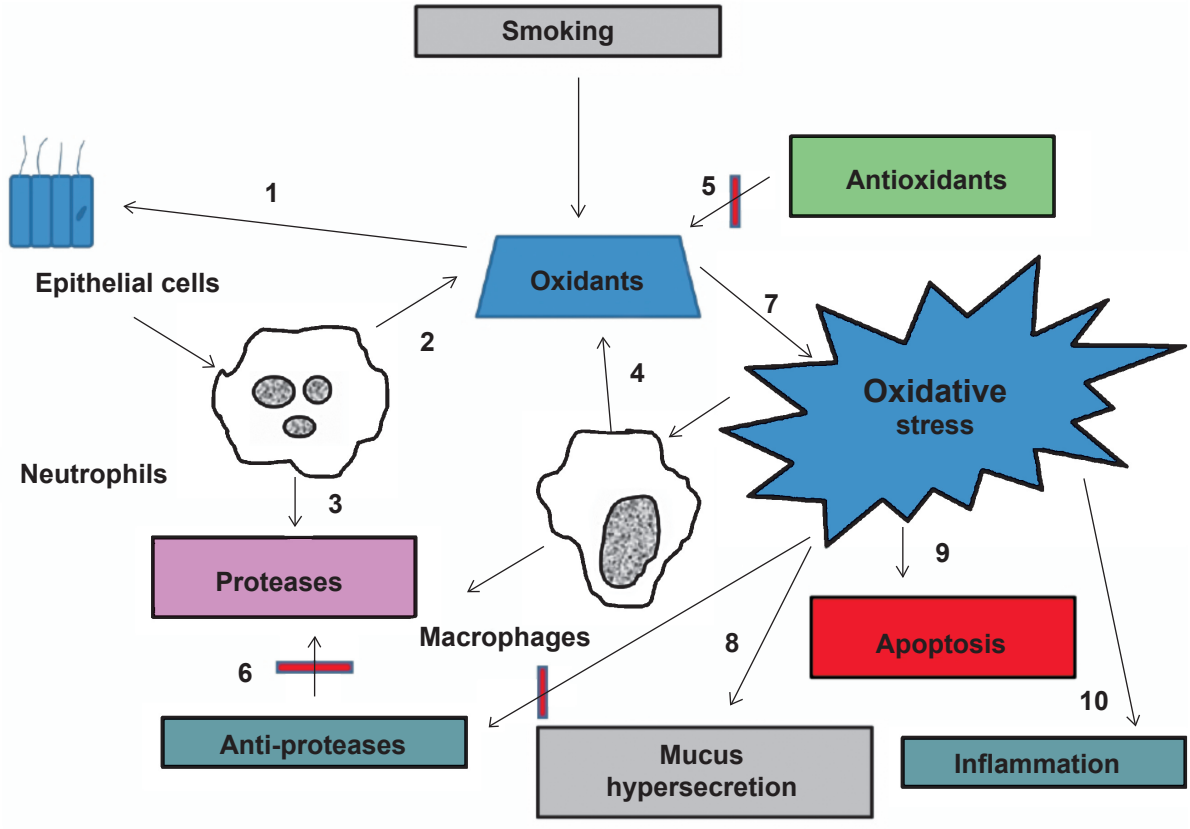

Fig. 1. Cigarette smoke is a complex mixture of thousands of chemical compounds including free radicles and oxidants. Cigarette smoke activates alveolar and bronchial epithelial cells (1) to elicit inflammatory responses leading to the release of cytokines and recruitment of neutrophils. Endogenous oxidants (2) and proteases (3) are generated from neutrophils and other phagocytic cells (macrophages) (4) increasing the oxidative burden in the lung. The lung has an efficient antioxidant (5) and anti-protease systems (6). The balance between the oxidants and the anti- oxidants is deranged by the exogenously and endogenously produced oxidants by the cigarette smoke leading to oxidative stress (7). Oxidative stress also contributes to mucus hypersecretion (8), apoptosis (9) and inflammation (10).

(acid-sensitive ion channels). The activation of these channels induces neurogenic inflammatory and brain-mediated responses of the airways. These responses compromise breathing and can lead to disease states if these persist. The TRPA1, a TRP ion channel expressed in chemosensory C-fibers, is activated by almost all oxidizing and electrophilic chemicals, including chlorine, acrolein, tear gas agents, and isocyanates. Chemicals likely activate TRPA1 through covalent protein modification[11].

Chemosensation to airways along with suitable reflex responses

Trigeminal chemosensory nerve endings in the nasal mucosa are in the first line of defense against noxious chemical challenges[12]. Calcitonin gene-related peptide (CGRP), tachykinins substance P (SP) and neurokinin A (NKA) released from chemically stimulated nerve endings, promote neurogenic inflammatory vasodilation and leakage, contributing to narrowing or obstruction of the nasal passages[13,14]. Vagal sensory nerves innervating the airways play a critical role in detection of the microenvironment in the airways. Oxidative stress and associated compounds activate unmyelinated bronchopulmonary C-fibers, initiating action potentials in these nerves that conduct centrally to evoke unpleasant sensations (*e.g.* urge to cough, dyspnoea, chest-tightness) and to stimulate/modulate reflexes (*e.g.* cough, bronchoconstriction, respiratory rate, inspiratory drive)[15]. Most of these factors are highly sensitive to intracellular calcium regulation in cells such as entry of nociceptors and other stimuli, highlighting the importance of Ca^{2+} transduction. The receptor-evoked Ca^{2+} signal causes Ca^{2+} release from internal stores, primarily the endoplasmic reticulum (ER), followed by activation of the store operated Ca^{2+} influx channels (SOCs) at the plasma membrane[11]. The two receptor stimulated SOCs, orai and transient receptor potential canonical (TRPCs) channels are gated by the ER Ca^{2+} sensor stromal interaction molecule 1 (STIM1)[16]. Also, the gating of peripheral terminal ion channels required for afferent nerve activation can occur through ionotropic and metabotropic mechanisms[17]. The ionotropic mechanism refers to an ion channel that has a self-contained activation/binding site for a specific stimulus (*e.g.* TRPV1 is directly gated by capsaicin). The metabotropic mechanism refers to the gating of certain ion channels downstream of second messenger systems (metabotropic), typically following the activation of G-protein-coupled receptors (GPCRs): for example, bradykinin, via the Gq-coupled B2 receptor can activate TRPV1 channels, inducing nerve depolarization and action potential discharge[18-20]. As COPD is characterized by epithelial cell damage, bronchoconstriction, lung parenchymal destruction and mucus hypersecretion, Ca^{2+} channels might impact COPD pathogenesis; because upon activation of TRP channel, these produce Ca^{2+} influx to trigger a variety of important physiological activities in the airways[21].

The respiratory airways have a ramified network of peripheral sensory neurons expressing chemosensory receptors, including members of the TRP ion channel family. The TRP channels are expressed in all these tissues especially on lung epithelium and smooth muscles and are known to get activated by stimuli such as cigarette smoke, industrial pollutants, chlorine, aldehydes, and scents, which trigger the onset of such disease state. There exist 28 mammalian TRP channels which can be subdivided into seven main subfamilies on the basis of amino acid homology and are genetically conserved *viz*. the TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), and the TRPA (ankyrin) groups, of which six have been reported in *Homo sapiens*[22].

Each TRP channel subunit consists of six putative transmembrane spanning segments (TM 1–6), a pore-forming loop between TM 5 and TM 6, and intracellular located-NH_2 and-COOH termini. Each of these channel subunits is either homo- or heterotetramers which results in the formation of cation-selective channels[22] to allow selective molecules to pass through them as depicted in Fig. 2.

Chronic obstructive pulmonary disease (COPD) and oxidative damage

Oxidative stress is the main reason behind COPD pathogenesis, as our lungs are being constantly bathed in oxidants. ROS is produced due to ageing as a result of various endogenously-generated oxidants and catalysis by inhaled toxic particulates. Overproduction of ROS (arising either from mitochondrial electron-transport chain or excessive stimulation of NADPH) results in oxidative stress, a deleterious process that can be an important mediator of damage to cell structures, including lipids and membranes, proteins, and DNA[23]. However, ROS is also required by the body during normal physiological functions for elimination of pathogens and other toxic metabolites produced in the body. Thus the body is constantly subjected to a redox control, which on imbalance results in disturbed homeostasis, resulting in degradation of normal tissues[23].

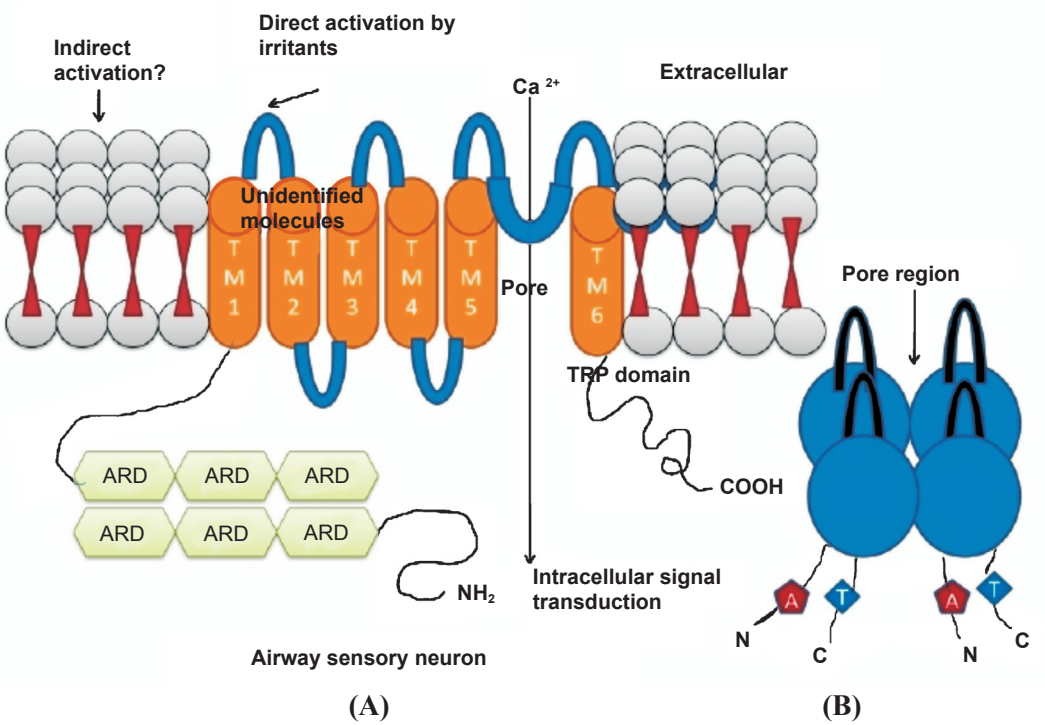

Fig. 2(A). A typical TRP channel containing six conserved transmembrane segments (TM1 to TM6) with a pore-forming reentrant loop between TM5 and TM6. TM1 carrying 6 ARDs (Ankyrin repeat domains); **(B).** the TRP pore structure formed of four subunits, each with six highly putative transmembrane helices. The pore contains a selectivity filter, which dictates through its stereochemical and electrostatic properties what kind of molecules are allowed through the pore.

Cigarette smoking has been a known factor responsible for development of COPD due to oxidant overload in the lower airways[9]. However, not all smokers develop COPD. The severity of COPD can be different among smokers with similar degree of exposure or no exposure. It is documented that lipid peroxidation occurs by the release of hydroxyl radicals by the cigarette smoke. These hydroxyl radicals react with unsaturated fatty acids of the membrane phospholipids to generate organic acid-free radicals which in turn react with oxygen to form lipid hydroperoxides. The latter act as free radicals, initiating an autocatalytic chain reaction and cause extensive membrane damage[24]. These are unstable compounds that tend to decompose rapidly to form secondary products which are responsible for deleterious effects of lipid peroxidation. These include alkanes, like ethane, pentane; and aldehydes, such as malondialdehyde. Among smokers, the thiobarbituric acid reactive substances (TBARS) levels were higher among those with COPD compared with those without COPD. These observations reflect increased lipid peroxidation because of oxidative stress due to smoking[25].

Risk factors of COPD in non-smokers may include genetic factors (such as alfa-1-antitrypsin deficiency), long-standing asthma, exposure to exogenous ROS *viz*. outdoor air pollution (from traffic and other sources), environmental smoke exposure (ETS), biomass smoke, occupational exposure, diet, recurrent respiratory infection in early childhood, tuberculosis and several such factors. In Asian region, indoor/outdoor air pollution and poor socio-economic status may play important roles in the pathogenesis of non-smoking-related COPD[25].

Alveolar macrophages of higher granular density are more prevalent in the lungs of smokers and leading to increased $O_2^{\bullet -}$ production[26,27]. The generation of ROS in epithelial lining fluid may be further enhanced by the presence of increased amounts of free ions in the airspaces in smokers[28,29].

An association between hydrogen peroxide (H_2O_2), superoxide anion, and hydroxyl radical is generate as byproducts of oxygen metabolism are released by peripheral blood neutrophils, resulting in bronchial hyper-responsiveness in patients with COPD[30].

Cell-derived ROS: In a metabolically active cell, the chief ROS-generating enzymes are NADPH oxidase, haem peroxidases (myeloperoxidase, MPO) or eosinophil peroxidase (EPO)[31]. Reactive nitrogen species (RNS), superoxide anion and H_2O_2 are also generated by mitochondria[32,33].

Environmental sources of ROS: Superoxide and nitric oxide generated from cigarette smoke[34] and atmospheric ozone exposure cause lipid peroxidation and inflammation of airway epithelium[35]. Further, heavy metal ions can cause damage to cellular nuclear proteins and DNA[36].

Role of TRP channels in chronic lung inflammation and onset of COPD

Exogenous pollutants act as lachrymatory agents, thus stimulating the corneal and airway passage nerves which are densely innervated by peripheral sensory nerve fibers (PSNF). These work by irritating mucous membranes that trigger the lachrymator reflex, ocular pain and blepharospasm after exposure to such noxious chemical stimulus[37]. Most TRP channels are located on plasma membranes (except nuclear membrane and mitochondrial membrane), where these have an essential role in the influx and/or transcellular transport of Ca^{2+}, Mg^{2+} and trace metal ions[38]. The mechanism of involvement of various TRP channels in various disease states is still not clear, however, the channels involved in patients with respiratory distress is shown in Table I.

Other indications of the involvement of TRPs in several diseases come from correlations between the levels of channel expression and disease symptoms or from the mapping of TRP-encoding genes to susceptible chromosome regions[41].

A study examining the role of TRPC6 on human alveolar macrophages and lung tissue macrophages reports an increase in the expression of TRPC6 mRNA in COPD patients as compared to other TRPs[39]. The pathophysiological role for non-neuronal TRPV1/TRPA1 is more apparent in the case of inflammation, infection and immunity. Though the effects of these TRP channels are non-neuronal, their impact is indirectly upon pain and/or neurogenic inflammation. While TRPV1 or TRPA1 activation causes airway neurogenic inflammation, non-neuronal TRPA1 produces an additional, prominent non-neurogenic inflammatory response, which may contribute to inflammatory airway diseases, offering a novel interpretation for the role of TRPA1 that could be a novel target for the treatment of inflammatory respiratory diseases[40]. TRP channels also play a role in the removal of foreign objects and irritants from lungs as Fig. 3 shows a simplified schematic diagram illustrating mechanisms and cell types with TRP expression in COPD progression. In lungs these are either found in sensory neurons (TRPA1 and TRPV1) and their activation results in altered vagal output and hence change respiratory pattern, blood flow and coughing or located in alveolar macrophages (TRPV2 and TRPV4) for initiation of an immune response[42].

TRPM4 and TRPM5, the Ca^{2+}- activated non-selective cation channels represent a molecular candidate for a large number of functionally similar Ca^{2+}-activated cation channels found in native cell types (phagocytic naïve cells) as a typical fingerprint, its lack of permeability for Ca^{2+} in the TRP superfamily. However, Ca^{2+} is a major regulator of their activity since both channels are activated by a rise in internal Ca^{2+} [43]. The function of TRPM4 has been suggested to result in inappropriate release of cytokines triggering immunological hyperresponsiveness, proinflammatory conditions, or allergy[22].

A potential mechanism to explain chronic cough in conditions where there is repeated or severe irritant-induced airway epithelial injury (*e.g.* RADS) is through persistent TRPV1 channel activation (*e.g.* TRPV1pathy) with accumulation of inflammatory mediators, tachykinins, and the release of neurotrophins leading to persistent cough and airway inflammation. The significance of this observation is that, if proven, it may provide new therapeutic approaches for the treatment of chronic cough[44].

TRPA1 is activated by tear gas agents, chlorine, reactive oxygen species, and noxious constituents of smoke and smog, initiating irritation and airway reflex responses. Together with TRPV1, the capsaicin receptor, TRPA1 may contribute to chemical hypersensitivity, chronic cough, and airway inflammation in asthma, COPD, and reactive airway dysfunction syndrome[45]. TRPA1 agonist activity of a given endogenous compound depends on its site of origin, reactivity, membrane permeability and reach, tissue antioxidant levels, and many other factors. TRPA1 is likely to

Table I. Involvement of various TRP channels in patients with respiratory distress

Channels	Subtypes with Ensemble protein IDs and chromosomal loci	Structure	Cellular expressions	Functions	Potential agonists	References
TRPV • Having 6 *Homo sapiens* subtypes. • All non-selective to cationic/ moderately to Ca^{2+}. Permeable ratio $P_{Ca}^{2+}/P_{Na}+$: ~1 to ~10	TRPV1 ENSP00000174621 Chr.17p13.3	Contains 3 to 5 ankyrin repeats in their cytosolic NH_2 termini.	Dorsal root and trigeminal ganglia; Airway sensory fibers lining the trachea, bronchi, alveoli, and nasal mucosa; spinal and peripheral nerve terminals, brain, skin (cutaneous sensory nerve fibers, mast cells, epidermal keratinocytes, dermal blood vessels, the inner root sheet and the infundibulum of hair follicles, differentiated sebocytes, sweat gland ducts, and the secretary portion of eccrine sweat glands), pancreas, bladder (urothelium, smooth muscle, blood vessels and neurons).	Thermo-sensation ≥43°C; autonomic thermoregulation; nociception; pain management; synaptic plasticity in the brain (long-term depression); endocannabinoid signaling in the brain; food intake regulation; growth cone guidance in the brain; osmosensing in the brain; multiple functions in the gut.	Bradykinin, prostaglandins, histamine, purines, proteases, nerve growth factor (NGF), chemokines, and many other proinflammatory mediators	11, 22, 37, 39
	TRPV4 ENSP00000261740 Chr.12q24.1	Contains 3 to 5 ankyrin repeats in their cytosolic NH_2 termini	CNS (large neurons), trigeminal ganglia, heart, liver, kidney, skin (keratinocytes), osteoblasts, blood vessels (endothelium), bladder (urothelium) and testis, cochlea (inner and outer hair cells, marginal cells of the cochlear stria vascularis), kidney (epithelial cells of tubules and glomeruli).	Thermo-sensation (moderate heat); mechano-sensation; osmo-sensation; nociception; low pH, modulation of cell migration; endothelium vaso-motor control and possible shear stress sensor; urothelium voiding control; osteogenesis and osteoclast function; neurodegenerative diseases; control adherens junctions in skin; cochlea	Bradykinin, prostaglandins, histamine, purines, proteases, NGF, chemokines, and many other proinflammatory mediators	22, 37, 39

Contd...

Channels	Subtypes with Ensemble protein IDs and chromosomal loci	Structure	Cellular expressions	Functions	Potential agonists	References
TRPA •Having only 1 *Homo sapiens* subtype. •All permeable to cations/Ca^{2+}. Permeable ratio P_{Ca2+}/P_{Na+}: 0.8–1.4	TRPA1 ENSP00000262209 Chr.8q13	Exhibits 14 NH_2 terminal ankyrin repeats, presumed to play a role of mechano-sensor.	Hair cells, sensory dorsal root and trigeminal ganglia neurons, fibroblasts.	Thermo-sensation (noxious cold) (-70°C); the most versatile chemo-sensor activated by isothiocyanates (pungent element in mustard oil, wasabi, and horseradish), methyl salicylate (winter green oil), cinnamaldehyde (cinnamon), allicin and diallyl disulphide (garlic), acrolein (irritant in vehicle exhaust fumes and tear gas), and Δ9 tetra-hydrocannabinol (Δ9THC, the psychoactive compound in marijuana) ; cold-induced contraction in colon and bladder	Reactive oxygen species (ROS), hypochlorite, lipid peroxidation products, cyclopentenone prostaglandins, and isoprostanes.	11, 22, 37, 40
TRPC •Having 6 *Homo sapiens* subtype. •Non-selective/ moderately selective to Ca^{2+}-permeable cation channels, •Permeability ratio (P_{Ca}^{+2}/P_{Na}^{+}) varies significantly between different members of the family.	TRPC1 ENSG00000144935 Chr. 3q22-q24	A structural motif in the COOH-terminal tail, the TRP box, which is located close to the intracellular border of S6 and contains the invariant sequence EWKFAR. TRPC channels also contain 3 or 4 NH_2-terminal ankyrin repeats	Ubiquitous	Generation of the excitatory postsynaptic potential in brain; netrin-1 and brain-derived neurotrophic factor (BDNF)-mediated growth cone guidance; connections to sleep/wakefulness states, alertness and appetite; brain development (together with TRPC5); glutamate signaling in hippocampus; regulation of smooth muscle contraction, pulmonary system; platelet function; skeletal muscle differentiation; mechano-sensation?	Protein kinase C (PKC)/ diacylglycerol (DAG)/ intracellular Ca^{2+}, store depletion, 20-HETE, 20-hydroxyeicosatetraenoic acid/1-oleoyl-2-acetyl-sn-glycerol (OAG)	22, 40

Contd...

Channels	Subtypes with Ensemble protein IDs and chromosomal loci	Structure	Cellular expressions	Functions	Potential agonists	References
	TRPC3 ENSP00000368966 Chr.4q25-q27	A structural motif in the COOH-terminal tail, the TRP box, which is located close to the intracellular border of S6 and contains the invariant sequence EWKFAR. TRPC channels also contain 3 or 4 NH_2-terminal ankyrin repeats	Central nervous system (CNS) and smooth and cardiac muscle cells	BDNF-mediated growth cone guidance (TRPC1-independent); spine formation in brain; γ-amino butyric acid signaling in striatum; astrocyte function; motor control in cerebellum; cerebral vasomotor control; erythropoietin function; functional coupling to orexin receptor	PKC/DAG/intracellular Ca^{2+}, store depletion, 20-HETE, 20-hydroxyeicosatetraenoic acid/OAG	22, 40
	TRPC6 ENSP00000340913 Chr.11q21-q22	A structural motif in the COOH-terminal tail, the TRP box, which is located close to the intracellular border of S6 and contains the invariant sequence EWKFAR. TRPC channels also contain 3 or 4 NH_2-terminal ankyrin repeats	Smooth muscle cells, lung, brain, placenta, kidney, spleen, ovary and small intestine, neutrophils.	Vasomotor regulation; α1 signaling in smooth muscle; smooth muscle proliferation; angiogenesis; endocannabinoid signaling in the brain; promotion of dendrite growth and synapse forming in the developing brain; glomerular filter integrity in the kidney; platelet function; redox sensor; mechano-sensor?	PKC/DAG/intracellular Ca^{2+}, store depletion, 20-HETE/OAG	22, 37, 39
	TRPC7 ENSP00000426070 Chr.5q31.2	A structural motif in the COOH-terminal tail, the TRP box, which is located close to the intracellular border of S6 and contains the invariant sequence EWKFAR. TRPC channels also contain 3 or 4 NH_2-terminal ankyrin repeats	Pituitary glands, kidney and CNS (human); heart and lung	Controls respiratory rhythm activity in pre-Bötzinger complex in the brain	PKC/DAG/intracellular Ca^{2+}, store depletion, 20-HETE/OAG	22, 37, 39

Contd...

Channels	Subtypes with Ensemble protein IDs and chromosomal loci	Structure	Cellular expressions	Functions	Potential agonists	References
TRPM. • Having 8 *Homo sapiens* subtypes. •All non-selective to cationic/moderately to Ca^{2+}. Permeable ratio P_{Ca2+}/P_{Na+}: 0.5-1.6	TRPM2 ENSP00000381023 Chr.1q22.3	These do not contain Ankyrin repeats within their NH_2-terminal domain. An exceptional structural feature is the presence of entire functional enzymes in their COOH termini: TRPM2 contains a functional NUDT9 homology domain exhibiting ADP-ribose pyrophos-phatase activity.	Brain, bone marrow, peripheral blood cells granulocytes and monocytes, lung, spleen, eye, heart and liver.	Oxidative and nitrosative stress response; activation of granulocytes; pancreas insulin release; critical in apoptosis	ADP-ribose, cADPR, NAD, heat, H_2O_2 and other ROS, inhibition of PARP-1	22, 37, 39

TRPA, transient receptor potential cation channel, subfamily A, member 1; TRPV, transient receptor potential channels vanilloid; TRPM2, transient receptor potential cation channel, subfamily M, member 2; TRPC, transient receptor potential cation channels; NUDT9, nudix (nucleoside diphosphate linked moiety X)-type motif 9

be activated or sensitized by a diverse cocktail of simultaneously present oxidants and electrophiles than by a single predominant agonist. This idea relates to the concept of the "inflammatory soup" describing the diverse mix of chemical and biological mediators promoting sensory neuronal sensitization and activation during tissue injury and inflammation[46]. It appears that endogenous oxidants and electrophiles need to be added to this particular mix[45].

TRPA1 and TRPV1: an overprotective mechanism?: TRPA1 is expressed in vagal sensory nerves and in the sensory nerve fibers originating from the dorsal root ganglion (DRG), thus innervating the airways. TRPA1 receptors are co-expressed with TRPV1 in a subpopulation of primary afferent somatosensory neurons innervating mouse airways and containing the neuropeptides SP, NKA and CGRP[47]. TRPA1 in the airway nerve endings is activated by pungent plant constituents such as allicin (garlic), cinnamaldehyde (cinnamon), and isothiocyanates (horseradish)[48-50] as well as from several volatile irritants and air pollutants such as formaldehyde[51] and acrolein[48]. Various endogenous byproducts derived from peroxidation of membrane phospholipids, such as 4-hydroxy-2-nonenal (4-HNE) and 4-oxononeal (4-ONE) have been described to activate TRPA1 and, as a consequence, produce pain and neurogenic inflammation[52]. Given the pathophysiological relevance of the endogenous activators of TRPA1, a role for this receptor in mediating pulmonary inflammatory processes characterized by oxidative stress can be predicted[53].

Among TRPA1 activators are some of the most harmful environmental/industrial irritants which, when inhaled, may cause a number of adverse reactions in the lung/airways, collectively known as RADS (reactive airways dysfunction syndrome)[54]. Therefore, TRPA1 can be considered either a chemoreceptor for environmental irritants or a mediator of neurogenic inflammation responses elicited by endogenous harmful stimuli in the airways.

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) activators of TRP channels: Pulmonary oxidant burden can be increased by infiltrating eosinophils, neutrophils and macrophages into alveolar space thereby generating ROS burden such as oxygen radicals (O_2•–), hydrogen peroxide (H_2O_2) and hypochlorite. On imbalance between oxidants and antioxidants (oxidative stress), ROS produced in excess generate highly reactive nitrogen species (RNS), like

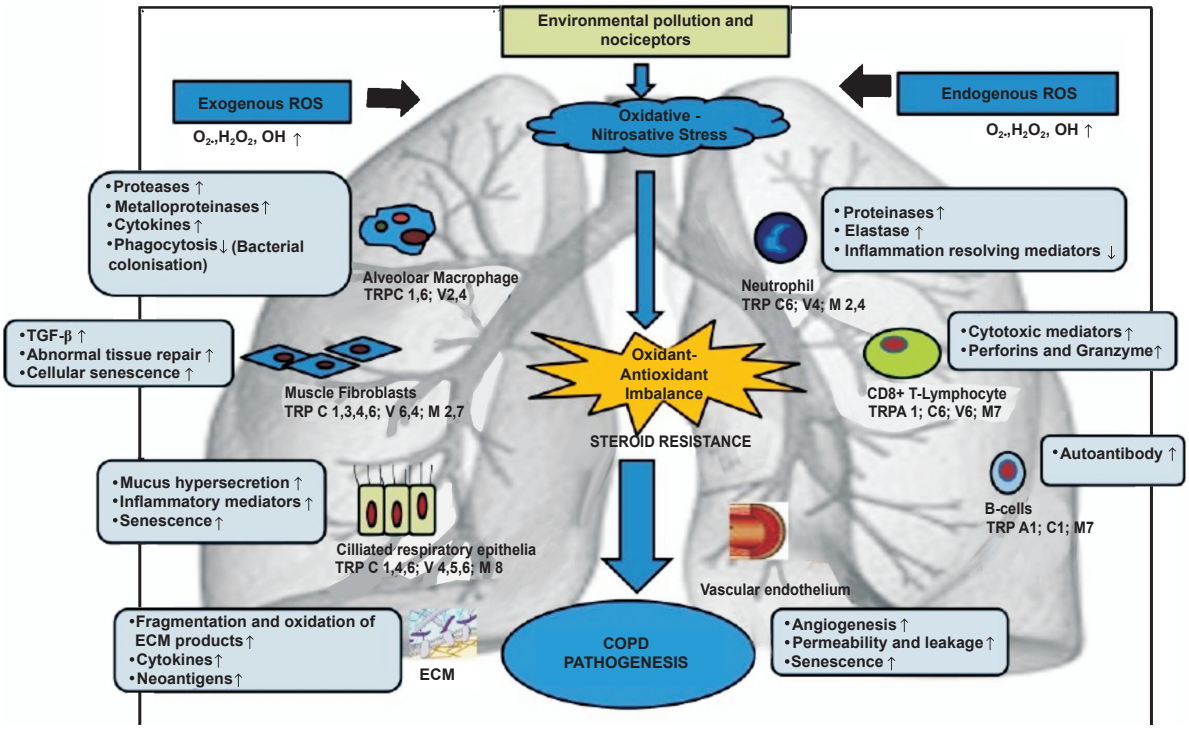

Fig. 3. A simplified schematic diagram illustrating mechanisms and cell types with transient receptor potential (TRP) expression which are thought to be involved in the pathogenesis of COPD. Inhaled exogenous pollutants enter lungs causing oxidative/nitrative stress, resulting in activation of various cell types alongwith TRP expression. ROS reactive oxygen species; ↑ increase; ↓ decrease; OH· hydroxyl radical; H_2O_2 hydrogen peroxide; TGF-β, transforming growth factor- β; ECM, extra cellular matrix; TRPCs, transient receptor potential canonical.

Table II. Antagonists representing potential antitussive and anti-inflammatory therapeutics for various respiratory airway diseases

TRP channel	Compound	References
TRPV1	Di(arylalkyl)- and aryl(aryl alkyl)urea [SB-452533]	60-62
	Di(arylalkyl)- and aryl(arylakyl)urea [ABT-102]	
	Cinnamides [SB-366791]	
	Quinazolinone compound 26	
	Capsazepine	
	Cinnamides [AMG-9810]	
	Carboxamides[SB-782443]	
	Ruthenium red	
	Imidazole derivatives [AMG517]	
TRPA1	Camphor and related compounds	61, 62
	Ruthenium red	
	HC-030031	
	AP-18 ([Z]-4-[4-clorophynyl]-3-methylbut-3-en-2-oxime	
	(1E, 3E)-1-(4-fluorophenyl)-2-methyl-pent-1,-3-one oxime	

Pubchem chemical names are given in parentheses
TRPV1, transient receptor potential channels vanilloid; TRPA1, transient receptor potential cation channel, subfamily A, member 1

peroxynitrite ($ONOO^-$) and nitrogen dioxide (NO_2), by reacting with nitric oxide (NO) which is overproduced in inflamed tissues, thus causing nitrative stress which is associated with various airway diseasess[55].

A typical target of ROS/RNS signaling is Ca^{2+} channels (TRPA1/V1) which mediate both long-term as well as acute cellular responses to oxidative stress. RNS similar to ROS directly attack unsaturated fatty acids (*e.g.* oleic acid) of membrane proteins, by adding NO_2 groups (nitration) to the organic acids[56], thereby generating highly reactive electrophilic compounds such as nitro-oleic acid[57]. RNS have the ability to directly activate TRPA1 by oxidation of key cysteine residues within the N-terminal sequence of the channel[58]. Similarly, ROS is also known to activate TRPA1 by oxidative modification of the key cysteines of the channel. TRPA1 is not only sensitive to electrophiles, but is also activated by oxidizing agents entering the airways.

Oxidative stress a well known indicator of acute and chronic airway inflammation, produces ROS during oxidant exposures and through catalysis by inhaled toxic particulates thus results in inflammation caused by infiltrating macrophages and neutrophils. Similar to the oxidant gas chlorine, ROS such as hydrogen peroxide excite airway sensory nerve fibers, resulting in respiratory depression[59].

There are several RNS derived from NO *viz*. peroxynitrite ($ONOO^-$) with high biological activity, formed from NO and O_2- One such product is 3-nitrotyrosine (3-NT), which can be used as a marker of $ONOO^-$ formation *in vivo*. Lipid peroxidation is an autocatalytic pathway that causes oxidative damage to cell membranes and results in the release of reactive lipid aldehydes. These cytotoxic metabolites such as 4-HNE diffuse from the site of production and react with cellular macromolecules. These in turn activate TRPA1and elicit hypersensitive reactions. Thus, ROS signals may alter behaviour of TRP channels[60].

Antagonists/drugs modulating TRP expression

Intense efforts have been carried out to design both competitive and non-competitive TRPV1 antagonists. Thus, drugs to modify TRP channels may be useful targets in asthma, COPD and other airway diseases. Antagonists that bind to the agonist binding site, and lock the channel in the closed, non-conductive state are known as competitive antagonists[61]. On the other hand, antagonists that interact with additional binding sites on the receptor structure preventing receptor opening by the agonist or in other words, blocking its aqueous pore fall under the category of non-competitive antagonists. Non-competitive antagonists acting as open channel blockers are therapeutically attractive because of their recognition of over-activated TRPV1 channels, which can reduce the potential of unwanted side effects, preventing receptor opening by the agonist or blocking its aqueous pore[60]. Despite the structural heterogeneity of TRPV1 antagonists, a general model for their binding interaction with TRPV1 antagonists has been proposed[62]. In brief, the unifying structural feature of TRPV1 antagonists is the presence of a central hydrogen-bond acceptor/donor motif flanked by a lipophilic side chain on one side and a more polar aromatic group that incorporates a hydrogen-bond acceptor on the other. A hydrogen-bonding motif is present in most known TRPV1 antagonist structures[63]. In the classic antagonists, the central core can act as an H-bonding donor and acceptor, whereas in some non-classic antagonists, it can only act as an H-bonding acceptor. Inflammatory response to cigarette smoke is mediated entirely by neuronal TRPA1. Therefore, TRPV1 and TRPA1 antagonists may represent potential antitussive and anti-inflammatory therapeutics for respiratory airway diseases, as illustrated by Vriens and co-workers[62] (Table II) .

Although the development of antagonists has been slow, but there is increasing interest in TRPA1 being used as a therapeutic target. One of these is the non-selective cation channel blocker ruthenium red, which, although described to be a potent blocker, is not selective and blocks several of the TRP channels, including TRPV1. Identification of toxicity issues has prevented the development of this compound. Interestingly, (±) camphor and related compounds have also been reported to be weak TRPA1 antagonists[64,65]. Potential therapeutic utility of TRPV1 antagonists in somatic pain, migraine, respiratory disease, bladder and gut related pain has been suggested[66,67].

In 2007, GlaxoSmithKline disclosed its Phase 1 results obtained with its selective and potent TRPV1 antagonist, SB-705498. In the first part of the study, single doses of SB- 705498 ranging from 2 to 200 mg did not display efficacy in the capsaicin-evoked flare test[68]. However, in the second part of the study, a single oral dose of 400 mg SB-705498 substantially reduced pain from cutaneous capsaicin challenge (0.075% capsaicin cream applied to the forearm) compared to placebo. Importantly, SB-705498 did not show any serious adverse effects in the study. Topical formulations

of SB-705498 have been recently evaluated in two Phase 2 clinical trials in chronic cough and non allergic rhinitis patients[69]. Another Phase 1 trial was started in 2011 with topical formulation in pruritus[70].

Gene controlling exacerbation of COPD

An interaction between gene and various environmental factors may be responsible for distinct aberrant pathophysiological processes/pathways. Like many chronic complex diseases, it has been difficult to unravel the genetic predisposition and pathogenetic mechanisms for COPD. Pulmonary function is influenced by heredity[71,72]. There is also familial aggregation of COPD, indicating probable heritability of risk factors for the disease[72]. It is still obscure how genetic factors contribute to the development and progression of COPD. Exogenous pollutants have pleotrophic effects on human bronchial epithelium as they coordinate recruitment of pivotal inflammatory cells in several pathologies, including chronic COPD[73].

Case control studies suggested associations between COPD and polymorphisms of the alpha1-antitrypsin, tumour necrosis factor alpha (TNFα), and surfactant protein B genes[74-76]. In a study on Central Indian population, genetic alteration has been found to be one of the late effects of industrial pollutants, thereby increasing the susceptibility to COPD. This study showed microsatellite instability (MSI) to be weakly associated with smoking, age, and exposure to exogenous toxins, which are instrumental in the rise of COPD cases[77].

Candidate genes involved in established pathogenetic pathways have been investigated for their association with COPD (oxidative stress, protease-anti-protease imbalance, chemokines, cytokines, and extracellular matrix breakdown and repair). It has been documented that the importance of genetic factors in the development of COPD especially in the young, is attributed to alpha-1-antitrypsin (A1AT) deficiency, a protein required for inhibition of neutrophil elastase, proteinase 3 (PR3), cathepsin G, kallikreins, matriptase, caspase-3 and ADAM-17[3,78]. A1AT encoded by the *SERPINA1* gene, is a member of the serpine protease inhibitor super family (SERPIN), and is mainly produced by hepatocytes. Some candidate genes have been identified, such as *ADRB2, CHRNA5, CSF3, EPHX1, GSTO2, HMOX1, MMP12, SERPINA1, SERPINE2, SFTPB, SMOC2, TGFB1, TNF, IL1RN/IL1B, IL4R, IL6, IL8, IL10, INF-γ, ADAM33, MMP1, SOD3, GSTP1, GSTT1* and *GSTM1*[79-84].

Studies on $TRPV4_{P19S}$, a human genetic polymorphism previously identified as a COPD susceptibility locus[21], displayed an increase in *MMP-1* (matrix-metalloproteinase) activation via increased Ca^{2+} influx, providing a mechanistic link between human airway epithelium signaling, airway disease, and air pollution. The TRPV4 is expressed in ciliated bronchial epithelial cells where it is believed to play a pivotal role in regulating ciliary movements[85]. This function of TRPV4 is one possible mechanism that may explain the genetic association between multiple TRPV4 SNPs (single nucleotide polymorphismsims) and COPD. The COPD-associated $TRPV4_{P19S}$ SNP located in the coding region (C144T) in exon 2, at the N-terminal of the ankyrin repeats, results in change in charge from non-polar to polar causing less conductivity, and thus displays gain-of-function characteristics in human airway epithelial cells, where it increases Ca^{2+} influx and secretion of matrix metalloprotease-1 in response to diesel exhaust[21,86,87]. The increased intracellular Ca^{2+} may compromise ciliary movements, leading to accumulation of harmful particles in the lungs. If clinically safe and effective inhalable TRPV4 antagonists are synthesized, these can be given preventively to at risk patients (*e.g.* heavy smokers) who carry COPD-associated TRPV4 mutations.

Overall this suggests a clinical benefit of inhibiting TRPV4 function in the treatment of altered lung function. Additional benefit is suggested in inhibiting TRPV4 function in pulmonary-based pathologies presenting with symptoms including lung oedema/congestion, infection, inflammation, pulmonary remodelling and/or altered airway reactivity. A genetic link between TRPV4 and COPD has been identified[21] suggesting potential efficacy for TRPV4 modulation in treatment of COPD with or without coincident emphysema. Expression of few TRP channels is enhanced in airway disease. Thus making them promising targets for the treatment of chronic cough[88].

Further studies are being carried on COPD patients by focusing primarily on genes involved in protease-anti-protease and oxidant-antioxidant pathways. However, given the diverse pathways (such as inflammation, innate immunity, cell death, matrix repair mechanisms and lung development) involved

in COPD pathogenesis it is likely that other genes contribute as well[78].

Conclusions & perspectives

TRP channels are emerging as vital cellular switches that allow us to sense our environment. Their multifunctional role as cellular sensors is important in understanding human pathophysiology and consequently disease development as well as progression. These can be potential drugs to curb the rampant progress of COPD especially in a sub-continent like India. Further understanding of the effects and roles of TRP channels/ROS in basic cellular functions as transduction of Ca^{2+}ions or amplification of pro-inflammatory and immunological responses, signaling pathways, activation of transcription factors, chromatin remodelling and gene expression will provide important information regarding basic pathological processes contributing to chronic lung diseases such as COPD. Identification of genes that predispose to the development of chronic lung diseases may identify novel therapeutic targets such as the genotypic/ phenotypic disposition of the population at large.

In summary, the oxidative stress is associated with the pathogenesis of various chronic lung diseases. Modulation of selected TRP channels may have beneficial effects at targeting key features of these respiratory diseases including airways inflammation, airways hyper-reactivity, mucus secretion and cough. Blockers of TRP channels may offer a useful strategy for curbing the exaggerated chemosensory responses accompanying these conditions, thereby reducing sensory irritation and, potentially, prevent adverse long-term health effects elicited by neurogenic inflammatory mechanisms.

Conflicts of Interest: None.

Acknowledgment

Authors thank Dr Manoj Pandey, Director, Bhopal Memorial Hospital and Research Centre, Bhopal for technical suggestions.

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