EC PULMONOLOGY AND RESPIRATORY MEDICINE
Perspective

Evolution and the Human Cough Reflex

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Received: November 20, 2017; **Published:** December 05, 2017

Abstract

The traditional theory of the human reflex cough proclaims there are two types of cough reflexes that evolve in humans. A mechanically-stimulated reflex cough becomes a protective mechanism against aspirated gastric content because the larynx moves to a closer proximity to the opening of the esophagus. Another reflex cough is instigated by chemicals and is defensive against lung infections and airborne irritants. As Earth becomes colder, human ancestors begin living closer together in larger social groups, in poorly ventilated enclosures and in close proximity to non-primate animals. There is a greater risk for infectious diseases as well as exposure to airborne irritants from burning fires within cave. On a molecular level, both types of cough response utilize transient receptor potential (TRP) vanilloid cation channel, TRPV1. An opposing theory stipulates that the combination of genetic and environmental happenings spur survival of a disappearing ascorbate-deficient hominid population by utilizing a previously evolved cough reflex and not one newly designed after anatomic changes from speech and locomotion. The Toba volcanic eruption, 74,000 years ago, spews massive airborne ash requiring coughing. When the Homo specie are near the brink of extinction, a life-saving particulate-clearing cough, previously evolved, is there for protection. Utilizing a Darwinian outlook, simply the most "fittest" endure the genetic and environmental challenges. An effective involuntary cough reflex and human ingenuity, help the fewer evolving hominids survive. Could the cough reflex have saved the human species from extinction?

***Keywords:** Human Cough Reflex; Evolution; TRP*

Introduction

The evolutionary theory proposes that the descent of all life derives from a last universal common ancestor; and that, natural selection led to Earth's biodiversity [1-3]. Evolution is the existing scientific theory explaining how and why life on Earth changes over time [4]. Ultimately what we know about human cough physiology is learned from animal experimentations; but, there is little to enlighten us as to how or why humans cough evolves to fit changes in humans' life and environment [5,6].

For evolving organisms, small advantageous genetic changes slowly accumulate over millions of years to become adapted by the population who then passes the genetic improvements on to successive generations bestowing them with a better life existence [7]. Replacement of members of successive generations may be by off-springs better adapted to survive and reproduce in their environment [8]. At a molecular level, heritable traits pass from one generation to the next by DNA encoding that conveys new or modified genetic information to off springs [9]. A genetic change may entail adapting an ancestral gene, both duplicated and mutated, to acquire a new function [10]. As part of the evolutionary process, highly conserved and unchanged ancient genes, preserved over millions of years, are repeatedly reused at different stages and in different parts of the developing human being [11]. The genes are guided by a cascade of regulatory and structural genes to create a precise pattern or function.

This manuscript, addressing human evolution and the human cough reflex, submits new theories and perspectives. A major focus of this manuscript is on the *Hominidae*, first living in Africa about 25 to 30 million years ago and also referred to as "great apes" or *Hominids*.

The latter designation includes extinct proto-human species such as *Australopithecus* and *Neanderthals* [2,12]. Primitive hominids subsequently evolve in to the human species (*Homo sapiens*). This manuscript does not focus on cough physiology, therapeutic modalities for cough suppression, details of chronic cough etiologies or other considerations about the coughing process, which are more thoroughly addressed in other publications [13-23].

Mammals

A nocturnal swimming mammal materializes about 225 million years ago. A warm-blooded placental (Eutherian) mammal splits from a marsupial mammal roughly 65 million years later and possesses a hindbrain and neocortex, hair, three middle ear bones, jaw point, occipital condyles, teeth as well as sweat glands; female mammals nurse their young off springs with milk secreted from their mammary glands. The devastating impact of a massive comet or asteroid causing the Cretaceous–Tertiary (K–T) extinction event happens 65 million years ago; it completely wipes out 75% of the plant and animal species on Earth (including dinosaurs) [24]. The global debris from the massive impact causes enough cloud of soot to block out the sun and create a prolonged nuclear winter with lowering environmental temperatures making it impossible for plants and plankton to carry out photosynthesis [25,26]. A remaining very small tree-climbing, insect-eating, furry-tailed mammal prospers after the dinosaurs are wiped out [27,28]. Over the next 43 million years, abundant new species fill the altered and emptied ecological niches shaped by the K-T extinction event and surviving mammals. Diversifying mammals evolve into new species such as horses, whales, bats, and primates [29]. It takes another 30 million years or more before there is a lineage split from a common primate ancestor creating two completely different animal types, the chimpanzee (Pan) and the Homo species. Serial hominid evolutionary intermediaries emerge over next 6 - 7 million years before the true *Homo sapiens* appears in Africa nearly 200,000 years ago [30].

The Fish Coughs

Hundreds of millions of years ago, the fish evolves a so-called cough-like interruption in their breathing cycle to clean their gills of accumulated particulate matter [31]. The unique maneuver may have been the harbinger of the future human cough reflex. Cough frequency increases after exposing fish to chemicals and effluents devoid of particulate matter [31]. In a somewhat similar manner, the human cough reflex clears the airways from foreign particles, fluids and microbes.

Prologue-Human Cough Reflex

As a prologue to the expansion of the human cough reflex, evolution becomes a major reason why the human cough reflex is designed in a way that makes it both susceptible to anatomic alterations and responsive to adversative stimuli [1,3,8,32]. Vast amount of time passes as the primitive cough reflex is transformed and shaped. Often, evolutionary changes are simply a reprocessing of ancient revisions. New adaptations may appear in the form of a mutation, some good and others bad. Extreme reorganizations of neural workings take place. Eventually, a transformed human cough is distinguished as a precisely timed, multifaceted, neuromuscular phenomenon with synchronous coordination between areas of the brain, afferent sensory nerves, supraglottic structures, diaphragm's muscular activity, actions of neck, chest wall and abdominal muscles as well as the participation of laryngeal abductor and adductor muscles [33-35]. Inexplicably, two seemingly different types of human coughs grow out of the primitive reflex cough, likely because of different reasons. The character and location of where cough receptors localize hinge upon the makeup of the evoking stimulus, the site of the respiratory tract being stimulated and perhaps other factors [36]. The first type of cough is provoked by stimulating mechanically-sensitive afferent sensory receptors mainly deposited in pharynx, larynx and tracheobronchial locations [17]. Perchance, this type of cough becomes indispensable for expectorating atmospheric particulate debris and pollution from the Toba extinction event. The second type of cough is activated by chemical molecules bestowed on more distal lung locations. It evolves as emerging humans gain closer social ties and inhabit enclosed environments that risk the potential of spreading airborne infectious diseases. The primitive cough reflexes change in response to evolutionary and environmental stressors so that after passage of millions of years, effective cough reflexes fit the Earth's involvements by other mammal such as the cat, dog, rabbit, ferret, cow, guinea pig, monkeys and apes. Regrettably, it is not currently known whether all extant mammals evolve the ability to cough [6,14]. The mouse does not display a cough reflex.

Introduction of vertically-walking bipedalism struggles with gravitational after-effects from aspiration and drainage. Body anatomic developments provide a rejoinder to speaking and learning language. Evolutionary advantages adapt both harmful and useful genetic mutations. There are adjustments as to how the cough occurs after nervous stimulation. There is significant growth and reorganization of the growing brainstem and cortex. The cerebral cortex contributes to the reflex cough by both detecting aspects of the instigating sensory stimulus as well as choosing the proper non-suppressible reflex cough response [37]. Both overlapping and typical features of the cortical control network exist between voluntary and evoked coughs. The reflex cough is suppressed during sleep and is downregulated with neurological disease of the cortex and subcortex [37]. In the final analysis, human hardiness for survival reigns supreme.

Imperative is the location as to where the afferent sensory cough receptors become located. Stimuli for coughing converge on extrathoracic locations of cough receptors that provide protections against inhaled ash particulates, acid reflux (acid pH) and post nasal drainage [38]. Human cough receptors also become located on the posterior wall of the trachea, pharynx, and carina. The receptors are less abundant in the distal airways and are absent beyond the respiratory bronchioles. Impulses from provoked cough receptors travel to a medullary "cough center" that is under the control of higher cortical centers; the higher centers generate efferent signals to the diaphragm, abdominal and intercostal muscles as well as other expiratory muscles to produce the cough [39].

Bipedalism

The adaptation of bipedal locomotion, appearing roughly 4 - 7 million years ago, takes place before the use of stone tools and the enlargement of the human brain [40]. The uniqueness of bipedalism provides special evolutionary advantages. The vertically-positioned body and horizontally-facing head allows a wider field of vision with improved detection of distant entities. Structurally, there is posterior movement of the foramen magnum to aid the upright stance. The ancestral human's movements using only the legs free the upper limbs for fine hand manipulation [41]. The now free upper extremities provide a capability of digging, grasping and holding weapons during combat. With the use of the freed upper extremities, the emerging humans learn to hunt, control fire, cook food and ultimately become cave dwellers [41-43]. A disadvantage of bipedalism is that it situates the evolving human in a vertical position with a straight back and unlocks the susceptibility of gravity's drainage effect on gastric, nasal and sinus secretions; no other primate maintains the sustained upright position. While the chimpanzee, the closest human relative, moves with a more horizontally-positioned body, it walks on all four limbs; it can only walk upright for short distances.

Speech and Language

Supposedly, no other species is genetically equipped with a language faculty as are humans [44]. Speech uses the same body tools as with breathing [45]. Emitted sounds require rapid opening and closing of the vibrating vocal cords launching numerous puffs of air [46]. Compared with non-human primates, humans have significantly better control of breathing through longer exhalations and short-term inhalations during speaking. Speaking requires use of intercostal and abdominal muscles in order to expand the thorax during inhalation before exhalation. The muscles concerned are markedly more innervated in humans than in nonhuman primates [47].

A major impact on the cough reflex occurs as the evolving human begins to speak; it requires major brain and body anatomic modifications. There are alterations in facial and lip muscles and makeup of the nose, jaw and teeth. There is the distinctive descent of the hyoid bone below the mandible. The larynx moves to a more posterior location below the nasopharynx.

Creating understandable oral messages depend upon humans' uniqueness of using their tongue, lips and vocal organs as instruments of communication [41,48]. Supposedly, the tongue is the most important speech articulator, followed by the lips. Important structural makeovers of the tongue and lips take place 50,000-100,000 years ago [49]. For humans, the tongue shortens in size and shifts further back into the mouth's cavity space [50]. Chimpanzees use flexible and maneuverable tongues for eating food but not for vocalizing. When a chimpanzee is not eating, fine motor control over its tongue is deactivated [51].

There is claim that anatomic restructuring of the supralaryngeal tract is imperative for understandable speech [46]. Supposedly, the primate ancestor possesses a supralaryngeal vocal tract without the horizontal dimension being longer than the vertical one. Without this ineffective arrangement, early hominids are incapable of producing a full range of sounds 16. As a necessity, the supralaryngeal vocal tract transforms into a smaller horizontal oral cavity proportionally placed (1:1) at a right angle with the vertical pharyngeal cavity leading to a different shaped supralaryngeal region (Figure 1) [46]. Early human ancestors such as *Homo erectus* and *Neanderthal* species possess supralaryngeal vocal tracts intermediate in shape between those of chimpanzees and humans and supposedly are incapable of speech.

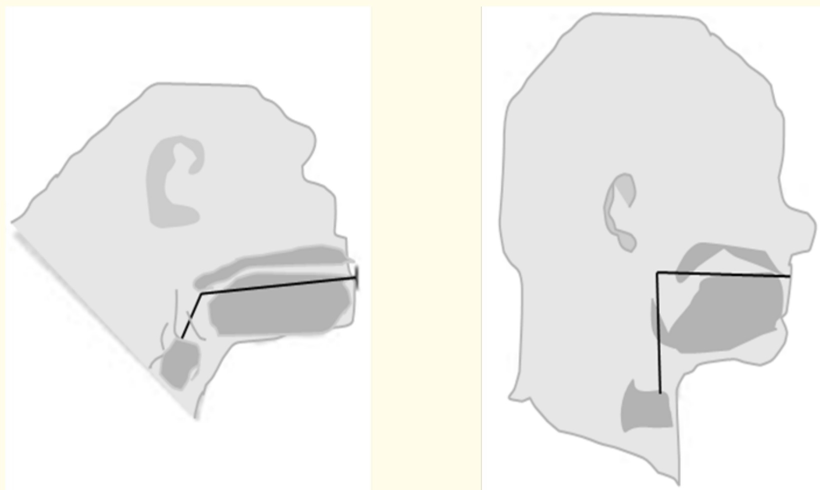

Figure 1: *The Homo species supra-laryngeal tract (right) is characterize by horizontal portion (i.e., mouth and oropharynx) forming a right angle of approximately equal lengths of 1:1 proportion with a vertical segment extending down from the palate to the vocal cords. In comparison, the chimpanzee (left) has a hyoid bone and larynx positioned at or near the base of the mandible; and, the tongue is long and mostly restricted to the oral cavity, resulting in a disproportionate supra-laryngeal vocal tract. Human ancestors such as Homo erectus and Neanderthal Chrono species possess supra-laryngeal vocal tracts intermediate in shape between those of chimpanzees and humans.*

Genes and Mutations

There are critical modifications of genes and occurrences of genetic mutations that impact the cough reflex. Beginning around 200,000 years ago, an adapted human $FOXP_2$ gene materializes to augment motor control and nervous activities vital for speech and crucial for the evolution of language [52]. Appreciating syntax, understanding semantics and gaining memory are imperative brain attributes for language and speech. The human $FOXP_2$ gene, in some way, assists the reflex cough [46,52,53].

Enhanced brain growth and neural reorganization is required for an effective human cough reflex. There is brain growth in the cerebral cortex after a genetic mutation introduces ASPM (Abnormal Spindle-like Microcephaly-associated) gene approximately 7 - 8 million years ago among ancestors of gorillas, chimpanzees and emerging humans [54-57]. Brain growth differs in humans compared to the chimpanzee. There is change in brain's shape during the human's first year of life when expanding neural circuits gain important clues from environmental changes.

A particular gene mutation becomes critical because of its potential for causing human extinction. Among evolving primates, a gene mutation leaves descendants totally dependent on dietary ascorbate intake. The mutation positions the metabolism of evolving humans away from most other mammalian species who retain the ability of endogenous ascorbate synthesis [58-60]. The genetic mutation in the liver causes a loss of the ability to synthesize L-gulano-γ-lactone oxidase, the final product of the four-enzyme biochemical scheme converting blood glucose into ascorbic acid (Vitamin C) [61-63]. Emerging humans are left with a non-functioning but encoding pseudogene

(Pseudogene ΨGULO) [64]. Without adequate exogenous vitamin C consumption, evolving humans are more likely to suffer from vitamin C deficiency and the adverse consequences of scurvy [63]. This hominid vitamin C deficiency is more likely to transpire during cold climates when vegetation containing vitamin C becomes sparse.

It Happens Again!

While evolution guides emerging humans' life on Earth, another major mass extinction event again takes place but this time conveying possible an unfavorable consequence for emerging humans. Roughly 74,000 years ago, a massive Toba super volcano eruption near Sumatra, spews trillions of tons of volcanic ash as well as releasing six billion tons of sulfur dioxide into the atmosphere. The volcanic eruption deposits an ash layer of about 6 inches thick over the whole of South Asia and deposits ash over the Indian Ocean, the Arabian Sea and the South China Sea [65]. Most of the ash and particulates falls within several miles near the volcano, but a significant portion travels a distance, drifting in the atmosphere for thousands of miles around the globe [66].

The Toba volcanic eruption occurs near the time emerging humans begin oral communications with each other [67]. It results in substantial global cooling and triggers a "volcanic winter" with a drop in the global mean surface temperature by 3 - 5°C and accelerates the transition from warm to cold temperatures of the last glacial cycle [66-68]. The colder climate affects vegetation on a global scale [60].

Living Together and Co-Evolution

The presence of two distinct afferent cough pathways is confirmed by animal experimentations; but, the phenomenon is less clear in humans [69-71]. How does one explain the cough reflex activated by chemicals and responsive to cough receptors buried in more distal airways? Closer social ties in poorly ventilated enclosures, increases the human risk of developing infectious diseases or suffering the brunt of airborne irritants. In theory, co-evolutionary arrangements sanction micro-organisms and their proto-human host to pursue a unique genetic arrangement [72]. Hypothetically, chemically-responsive receptors within the distal lung undergo genetic combinatorial diversification where a gene segment recombines with other gene segments to form a single unique gene capable of generating a diversity of chemical-responding receptors [73]. The re-worked system creates memory for the specific chemical [74]. Over time, the lung's memory system builds up a suitable library of highly specific responses to bacterial/viral chemical or irritant signals. The micro-organisms survive by spreading infective material to close hominid contacts via droplet nuclei ejected during coughing [75]. A suitable host response may be the release of neuropeptides and/or inflammatory molecules in response to chemical molecules [76,77].

Finale! The Human Cough Reflex

Maybe, the location and distribution of cough receptors undergo changes to meet anatomical modifications. Perhaps, the distally-located chemically-induced cough becomes part of a co-evolutionary accomplishment between humans and microorganisms. The Toba volcanic explosion generates a massive airborne particulate exposure necessitating expectorant-coughing for the fewer remaining evolving hominids beginning to master vocalization and language. Provocation by particulate ash stimuli instigates an expectorant cough [36,78]. A much colder climate is connected to diminishing vegetation for ascorbate deficient hosts. The collective situations impact the fewer breeding hominid population creating an evolutionary bottleneck that ultimately hastens the differentiation of the Homo species [68,79,80]. Emerging human species are nearly wiped out in many regions on Earth [60]. All humans alive today are descended from perhaps between 1,000 to 10,000 breeding pairs [68]. It is a reasonable conclusion to suggest that the combination of genetic, anatomic and environmental circumstances spur survival of the diminishing hominid population, possibly, in part, by providing a different type of cough at an important juncture in human evolution. Utilizing a Darwinian outlook, simply the most "fittest" endure the genetic and environmental challenges. An effective involuntary cough reflex and human ingenuity help the fewer evolving hominids survive. Could the cough reflex have saved the human species from extinction?

Conflict of Interest

I certify that I (Stuart M. Brooks, MD) am the guarantor and only corresponding author who holds no potential conflicts of interest; no sources of funding and support; no information on statistical analyses; correct name/participation/degree/institution of the only author. I also certify that I did not accept compensation for inclusion of any of the statements contained in the manuscript.

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