BioZone Pulmonary Drug Delivery System

Abstract

Methods for enhancing pulmonary pharmaceutical drug delivery are provided wherein the cumulative synergistic modalities are sequenced in a predetermined fashion for maximum effect.

Part One will provide a comprehensive discussion of the petitioned invention's ability to affect specific nerves of a mammal wherein intended modulation of neurotransmitters serve specific desired outcomes.

More specifically, Part One pertains to the petitioned invention's ability to intentionally modulate the electrical activity of specific nerves in a mammal wherein stimulation or suppression of neurotransmitter release, the balance of neurotransmitters in the brain, dilation of specific airways of the respiratory tract, and tidal volume exchange of air in the lungs are desirably affected.

Part Two will provide a comprehensive analysis and discussion of the petitioned invention's ability to selectively modulate the production of and viscosity of mucus in the respiratory tract, modulation of the mucociliary escalator of the lungs, enhance the permeability of the alveolar membrane and absorption of pharmaceutical agents across the alveolar-vascular interface, modulate specific inflammatory mediators and cascades, activate specific drug carriers, selectively deactivate leukocytes and platelets in the tissue and vasculature of the lungs, prevent cytokine storms and the destructive manifestations thereof, eliminate harmful accumulated inflammatory or infectious particulate debris in the lungs, promote DNA repair and cellular healing after irradiation,

More specifically, Part Two pertains to the petitioned invention's ability to provide specific cycled harmonic resonance frequencies, electron brush ionization, specific light wavelengths, specific acoustical stimulations, specific magnetic fields and magnetic drivers, specific pressure and thermal gradients, specifically modulate hemoglobin oxygen dissociation, specific hyper ultrasonic coupling, modulated dithermal discriminatory interference, specific vibratory and olfactory stimulations, and specific respiratory maneuvers; said provisions, in conjunction, facilitating the ability to deliver pharmaceutical agents through the respiratory system into the circulatory system and or specific tissues of said mammal.

Part One:

In one aspect the petitioned invention comprises a device positioned in contact with an outer skin surface of an individual or alternatively applied to a mucosal membrane, or in a combination thereof. An electric current is then generated external to the individual, via the device, therein transmitting the electric current transcutaneously in one application and transnasal or transbuccal in another application. Such electric current is predetermined in frequency and destined to affect specific nerves of the individual. Such predetermined frequency preferably between 500 Hz and 12,000 Hz and having a duty cycle between 0.5% and 12%.

The electrical current may include bursts of pulses having a burst duration of between 0.05 and 15 milliseconds and a burst frequency between 5 to 75 Hz. The mentioned method therein generating an electric field at the determined nerve or nerves above a threshold for generating action potentials within specific nerve fibers and below a threshold for generating action potentials within other fibers of the same nerve or nerves.

The described method is therein capable of supplying an electric current sufficient to generate an electric field above a threshold for generating an action fiber of the designated nerve which may be responsible for activating one or more neural pathways causing a modulation of a neurotransmitter within a brain, spinal cord, tissue, or organ of the individual. Said described method capable alone of being sufficient to generate a desired electrical field gradient at designated nerve or nerves of the individual. Such electric field is adequate to cause a release of either a stimulating or inhibitory neurotransmitter in the brain, spinal cord, tissue, or organ of the individual.

The method's described electrical field therein being adequate alone to cause an excitation or suppression of an excitatory neurotransmitter in said individual's anatomical structures. The described method may affect the excitatory neurotransmitter comprising at least one of a catecholamine or acetylcholine and whereby the inhibitory neurotransmitter may comprise at least one of GAMA, Serotonin, or Norepinephrine. Said method wherein the transmitting of such facilitates a sufficient level of the inhibitory neurotransmitter to be released in the brain to reduce a level of Glutamate in the brain. Said method wherein the inhibitory neurotransmitters are released onto airway-related preganglionic neurons of designated nerve or nerves to reduce the release of acetylcholine from the airway-related preganglionic neurons of said designated nerve or nerves. Said method is specifically applied such that the electric field is below the threshold for generating action potentials within specific fibers of determined nerve or nerves that in one instance may be responsible for modulating heart rate or blood pressure.

The mentioned device having an energy source comprising a signal generator and one or more electrodes coupled to the signal generator within the housing of the device. The described device potentially requiring a conducting medium within the housing between the electrodes and the electrically permeable contact surface. The device presented herein, generating said electrical current and electric fields therein activating said neural pathways and therefore modulating specific neurotransmitters of specific anatomical structures of an individual, therein exciting or inhibiting neurotransmitters which in turn cause specific effects on the body and structures of the individual.

Mentioned specific effects on the body and structures of the individual desirably and intentionally causing the relaxation of the bronchial tree of the respiratory tract of the individual therein causing the individual to inspire a greater tidal volume of air, said specific effects additionally causing a reduction in mucus production in the airways of the individual, a reduction in the viscosity of the mucus produced, an inhibitory effect on the cilia of the individual's respiratory tract, an increased permeability of the alveolar-capillary membrane and vascular endothelium, said effects promoting absorption of pharmaceutical drugs and or drug-carrier agents, said effects additionally providing an activation of said pharmaceutical drugs and or drug-carrier agents and or a desired deactivation of activated leukocytes or platelets, said deactivation of said leukocytes and platelets intentionally intervening in the release of certain cytokines and other mediators, said intervention decreasing inflammatory responses and potential damage to the macro and micro structures of the respiratory tract, said decrease potential of said methodology providing a similar beneficial result in the treatment of specific diseases and disease states as well as the facilitated pulmonary drug delivery aforementioned.

Background of the Invention

The field of the present invention in one aspect relating to the delivery of energy impulses (and/or fields) to bodily tissues for therapeutic purposes. The invention relates more specifically to devices and methods for enhancing drug delivery and absorption through an individual's pulmonary system yet additionally for treating conditions associated with bronchial constriction. The energy impulses (and/or fields) that are used to treat those conditions comprise electrical and/or electromagnetic energy, delivered non-invasively to the patient.

The use of electrical stimulation for treatment of medical conditions is well known. For example, electrical stimulation of the brain with implanted electrodes has been approved for use in the treatment of various conditions, including pain and movement disorders such as essential tremor and Parkinson's disease. Another

application of electrical stimulation of nerves is the treatment of radiating pain in the lower extremities by stimulating the sacral nerve roots at the bottom of the spinal cord.

Another example of electrical stimulation for treatment of medical conditions is vagus nerve stimulation (VNS, also known as vagal nerve stimulation). It was developed initially for the treatment of partial onset epilepsy and was subsequently developed for the treatment of depression and other disorders. The left vagus nerve is ordinarily stimulated at a location within the neck by first surgically implanting an electrode there and then connecting the electrode to an electrical stimulator.

Many such therapeutic applications of electrical stimulation involve the surgical implantation of electrodes within a patient. In contrast, devices used for the medical procedures that are disclosed herein do not involve surgery. Instead, the present devices and methods stimulate nerves by transmitting energy to nerves and tissue non-invasively. A medical procedure is defined as being non-invasive when no break in the skin (or other surface of the body, such as a wound bed) is created through use of the method, and when there is no contact with an internal body cavity beyond a body orifice (e.g., beyond the mouth or beyond the external auditory meatus of the ear). Such non-invasive procedures are distinguished from invasive procedures (including minimally invasive procedures) in that the invasive procedures insert a substance or device into or through the skin (or other surface of the body, such as a wound bed) or into an internal body cavity beyond a body orifice.

For example, transcutaneous electrical stimulation of a nerve is non-invasive because it involves attaching electrodes to the skin, or otherwise stimulating at or beyond the surface of the skin or using a form-fitting conductive garment, without breaking the skin. In contrast, percutaneous electrical stimulation of a nerve is minimally invasive because it involves the introduction of an electrode under the skin, via needle-puncture of the skin. In what follows, comparison is sometimes made between the disclosed noninvasive methods, versus comparable invasive methods, for purposes of demonstrating feasibility and/or validation of the noninvasive methods.

Another form of non-invasive electrical stimulation is magnetic stimulation. It involves the induction, by a time-varying magnetic field, of electrical fields and current within tissue, in accordance with Faraday's law of induction. Magnetic stimulation is non-invasive because the magnetic field is produced by passing a time-varying current through a coil positioned outside the body, inducing at a distance an electric field and electric current within electrically conducting bodily tissue. The electrical circuits for magnetic stimulators are generally complex and expensive and use a high current impulse generator that may produce discharge

currents of 5,000 amps or more, which is passed through the stimulator coil to produce a magnetic pulse. In contrast, the magnetic stimulators that are disclosed herein are relatively simpler devices that use considerably smaller currents within the stimulator coils. Accordingly, they are intended to satisfy the need for simple-to-use and less expensive non-invasive magnetic stimulation devices, for use in treating bronchoconstriction, as well as use in treating other conditions.

Potential advantages of such non-invasive medical methods and devices relative to comparable invasive procedures are as follows. The patient may be more psychologically prepared to experience a procedure that is non-invasive and may therefore be more cooperative, resulting in a better outcome. Non-invasive procedures may avoid damage of biological tissues, such as that due to bleeding, infection, skin or internal organ injury, blood vessel injury, and vein or lung blood clotting. Non-invasive procedures are generally painless and may be performed without the dangers and costs of surgery. They are ordinarily performed even without the need for local anesthesia. Less training may be required for use of non-invasive procedures by medical professionals. In view of the reduced risk ordinarily associated with non-invasive procedures, some such procedures may be suitable for use by the patient or family members at home or by first-responders at home or at a workplace. Furthermore, the cost of non-invasive procedures may be significantly reduced relative to comparable invasive procedures.

In the present application, the non-invasive delivery of energy is intended ultimately to dilate constricted bronchial passages of the lung, by relaxing bronchial smooth muscle and/or inhibit mucous production by the mucous glands. The smooth muscles that line the bronchial passages are controlled by a confluence of vagus and sympathetic nerve fiber plexuses. Spasms of the bronchi during asthma attacks, anaphylactic shock, and other pulmonary disorders can often be directly related to pathological signaling within these plexuses, as described below.

Asthma, and other airway occluding disorders resulting from immune responses and inflammation-mediated bronchoconstriction, affects an estimated eight to thirteen million adults and children in the United States. A significant subclass of asthmatics suffers from severe asthma. An estimated 5,000 persons die every year in the United States as a result of asthma attacks. Up to twenty percent of the populations of some countries are affected by asthma, estimated to be more than a hundred million people worldwide. Asthma's associated morbidity and mortality are rising in most countries despite the increasing use of anti-asthma drugs.

Asthma is characterized as a chronic inflammatory condition of the airways. Typical symptoms are coughing, wheezing, tightness of the chest and shortness of breath. Asthma is a result of increased sensitivity to foreign bodies such as pollen, dust mites and cigarette smoke. The body, in effect, overreacts to the presence of

these foreign bodies in the airways. As part of the asthmatic reaction, an increase in mucous production is often triggered, exacerbating airway restriction. Smooth muscle surrounding the airways goes into spasm, resulting in constriction of airways. The airways also become inflamed. Over time, this inflammation can lead to scarring of the airways and a further reduction in airflow. This inflammation leads to the airways becoming more irritable, which may cause an increase in coughing and increased susceptibility to asthma episodes.

In general, there are three mechanisms that may be triggered in acute asthma (and other conditions, such as anaphylaxis, as described below). First, allergens induce smooth muscle bronchoconstriction through Ig-E dependent release of mast cell mediators such as histamines, prostaglandins, and leukotrienes. Second, airway hyper-responsiveness resulting from local and central neural reflex stimulation and by mediators of inflammation can increase bronchoconstriction. A third mechanism may stimulate mucosal thickening and edematous swelling of the bronchial walls through increased microvascular permeability and leakage.

In the case of asthma, it appears that the airway tissue has both (a) a hypersensitivity to an allergen that causes the overproduction of the cytokines that stimulate the cholinergic receptors of the nerves and/or (b) a baseline high parasympathetic tone or a high ramp-up to a strong parasympathetic tone when confronted with any level of cholinergic cytokine. The combination can be lethal. Anaphylaxis appears to be mediated predominantly by the hypersensitivity to an allergen causing the massive overproduction of cholinergic receptor activating cytokines that overdrive the otherwise normally operating vagus nerve to signal massive constriction of the airways. Drugs such as epinephrine drive heart rate up while also relaxing the bronchial muscles, effecting temporary relief of symptoms from these conditions. Severing the vagus nerve (an extreme version of reducing the parasympathetic tone) has an effect similar to that of epinephrine on heart rate and bronchial diameter, in that the heart begins to race (tachycardia) and the bronchial passageways dilate.

Asthma is typically managed with inhaled medications that are taken after the onset of symptoms, or by injected and/or oral medications that are taken chronically. The medications typically fall into two categories: those that treat the inflammation, and those that treat the smooth muscle constriction. A first strategy is to provide anti-inflammatory medications, like steroids, to treat the airway tissue, reducing the tendency of the airways to over-release the molecules that mediate the inflammatory process. A second strategy is to provide a smooth muscle relaxant (e.g., an anticholinergic) to reduce the ability of the muscles to constrict. As treatments, anticholinergics improve lung function by modifying neural reflexes and parasympathetic vagal tone. While inferior to beta2-agonists as

a primary treatment, inhaled anticholinergics are effective as an adjunct to beta2-agonists and the combination offers an advantage in reducing hospital admissions.

It is sometimes advised that patients rely on anti-inflammatory medications and avoidance of triggers, rather than on the bronchodilators, as their first line of treatment. For some patients, however, these medications, and even the bronchodilators are insufficient to stop the constriction of their bronchial passages. Tragically, more than five thousand people suffocate and die every year as a result of asthma attacks .

Anaphylaxis ranks among the other airway occluding disorders as the deadliest, claiming many deaths in the United States every year. Anaphylaxis (the most severe form of which is anaphylactic shock) is a severe and rapid systemic allergic reaction to an allergen. Minute amounts of allergens may cause a life-threatening anaphylactic reaction. Anaphylaxis may occur after ingestion, inhalation, skin contact or injection of an allergen. Anaphylactic shock usually results in death in minutes if untreated. It is a life-threatening medical emergency because of rapid constriction of the airway, resulting in brain damage through oxygen deprivation.

The triggers for anaphylactic reactions range from foods (nuts and shellfish) to insect stings (bees), to medication (radio contrasts and antibiotics). It is estimated that 1.3 to 13 million people in the United States are allergic to venom associated with insect bites; 27 million are allergic to antibiotics; and 5-8 million suffer food allergies. In addition, anaphylactic shock can be brought on by exercise. Yet all such reactions are mediated by a series of hypersensitivity responses that result in uncontrollable airway occlusion driven by smooth muscle constriction, and dramatic hypotension that leads to shock. Cardiovascular failure, multiple organ ischemia, and asphyxiation are the most dangerous consequences of anaphylaxis.

Anaphylactic shock requires immediate advanced medical care. Current emergency measures include rescue breathing, administration of epinephrine, and/or intubation if possible. Rescue breathing may be hindered by the closing airway but can help if the victim stops breathing on his own. Clinical treatment typically includes administration of antihistamines (which inhibit the effects of histamine at histamine receptors, but which are usually not sufficient in anaphylaxis), and high doses of intravenous corticosteroids. Hypotension is treated with intravenous fluids and sometimes vasoconstrictor drugs. For bronchospasm, bronchodilator drugs such as salbutamol are administered.

The number of people who are susceptible to anaphylactic responses is estimated to be more than 40 million in the United States. Given the common mediators of both asthmatic and anaphylactic bronchoconstriction, it is not surprising that asthma sufferers are at higher-than-average risk for anaphylaxis. Tragically, many

of these patients are fully aware of the severity of their condition, but nevertheless die while struggling in vain to manage the attack medically. Many of these fatal incidents occur in hospitals or in ambulances, in the presence of highly trained medical personnel who are powerless to break the cycle of inflammation and bronchoconstriction (and life-threatening hypotension in the case of anaphylaxis) affecting their patient. Unfortunately, prompt medical attention for anaphylactic shock and asthma are not always available. For example, epinephrine is not always available for immediate injection. Even in cases where medication and attention is available, life-saving measures are often frustrated because of the nature of the symptoms. Constriction of the airways frustrates resuscitation efforts, and intubation may be impossible because of swelling of tissues. Typically, the severity and rapid onset of anaphylactic reactions does not render the pathology amenable to chronic treatment but requires more immediately acting medications. Epinephrine is among the most popular medications for treating anaphylaxis, commonly marketed in so-called “Epipen” formulations and administering devices, which potential sufferers carry with them at all times. In addition to serving as an extreme bronchodilator, epinephrine raises the patient's heart rate dramatically in order to offset the hypotension that accompanies many reactions. This cardiovascular stress can result in tachycardia, heart attacks and strokes.

Chronic obstructive pulmonary disease (COPD) is a major cause of disability and is the fourth leading cause of death in the United States. More than 12 million people are currently diagnosed with COPD. An additional 12 million likely have the disease but are unaware of their condition. COPD is a progressive disease that makes it increasingly difficult for the patient to breathe. COPD can cause coughing that produces large amounts of mucus, wheezing, shortness of breath, chest tightness and other symptoms. Cigarette smoking is the leading cause of COPD, although long term exposure to other lung irritants, such as air pollution, chemical fumes or dust may also contribute to COPD. In COPD, there is abnormally low air flow within the bronchial airways for a variety of reasons, including loss of elasticity in the airways and/or air sacs, inflammation and/or destruction of the walls between many of the air sacs and overproduction of mucus within the airways.

The term COPD includes two primary conditions: emphysema and chronic obstructive bronchitis. In emphysema, the walls between many of the air sacs are damaged, causing them to lose their shape and become floppy. This damage can also destroy the walls of the air sacs, leading to fewer and larger air sacs instead of many small ones. In chronic obstructive bronchitis, the patient suffers from permanently irritated and inflamed bronchial tissue that is slowly and progressively dying. This causes the lining to thicken and form thick mucus, making it difficult to breathe. Many of these patients also experience periodic episodes of acute

airway reactivity (i.e., acute exacerbations), wherein the smooth muscle surrounding the airways goes into spasm, resulting in further constriction and inflammation of the airways. Acute exacerbations occur, on average, between two and three times a year in patients with moderate to severe COPD and are the most common cause of hospitalization in these patients, with mortality rates of approximately 11%. Frequent acute exacerbations of COPD cause lung function to deteriorate quickly, and patients never recover to the condition they were in before the last exacerbation. As with asthma, current medical management of these acute exacerbations is often insufficient.

Exercise-induced bronchospasm (EIB) results from a transient increase in airway resistance that occurs five to ten minutes after initiation of exercise. It produces symptoms such as shortness of breath, cough, wheezing, chest tightness, or pain. Eighty to ninety percent of patients with asthma also have EIB, but up to a quarter of non-asthmatic athletes may also experience EIB. The condition is usually treated with short-acting bronchodilator medication, with or without the addition of anti-inflammatory agents, taken 15 to 30 minutes before initiation of exercise. However, many patients do not respond to those treatments, or they experience unwanted side effects. Accordingly, one objective of the present invention is to provide an alternative to pharmacological treatment, through the use of noninvasive vagal nerve stimulation before and/or after exercise.

Bronchospasm is one of the most significant respiratory complications that can occur during surgical anesthesia, and asthmatic patients, as well as some patients with COPD, are at elevated risk for it. Because the beneficial effects of steroids on airway reactivity occurs over a period of hours, patients at risk of experiencing bronchospasm during surgery are sometimes treated with steroids starting 24-48 h before surgery. The patients who are actually wheezing before surgery also receive treatment with inhaled beta-2 adrenergic agents and corticosteroids. Such wheezing may also be experienced by patients without pre-existing reactive airway disease, due to pulmonary edema, pneumothorax, drug reactions, aspiration, and endobronchial intubation. If the pharmacological treatment does not stop or prevent the wheezing, the surgery may be deferred, but this is not always practical or possible in view of the need for surgery. Accordingly, one objective of the present invention is to provide an alternative to pharmacological treatment, through the use of noninvasive vagal nerve stimulation before surgery.

Despite precautions and pre-treatments, bronchospasm may nevertheless occur during surgery, in which case, beta-2 adrenergic agents may also be administered through an endotracheal tube. For some patients, those agents may not be effective or are otherwise contraindicated, and the bronchospasm may continue even after the surgery is completed. Accordingly, another objective of the present invention is

to provide an alternative to pharmacological treatment for bronchospasm that occurs during and after surgery, through the use of noninvasive vagus nerve stimulation.

Unlike cardiac arrhythmias, which can be treated chronically with pacemaker technology, or in emergent situations with defibrillators (implantable and external), there is no commercially available medical equipment that can chronically reduce the baseline sensitivity of the smooth muscle tissue in the airways, to reduce the predisposition to asthma attacks, to reduce the symptoms of COPD or to break the cycle of bronchial constriction associated with an acute asthma attack or anaphylaxis. Therefore, there is a need in the art for new products and methods for treating the immediate symptoms of bronchial constriction resulting from pathologies such as anaphylactic shock, asthma, COPD, exercise-induced bronchospasm, and post-operative bronchospasm. In particular, there is a need in the art for non-invasive devices and methods to treat the immediate symptoms of bronchial constriction.

Although energy has been applied previously to patients in such a way as to bring about bronchodilation, those investigations involve methods that are invasive. For example, U.S. Pat. No. 7,740,017, entitled Method for treating an asthma attack, to DANEK et al., discloses an invasive method for directing radio frequency energy to the lungs to bring about bronchodilation. U.S. Pat. No. 7,264,002, entitled Methods of treating reversible obstructive pulmonary disease, to DANEK et al., discloses methods of treating an asthmatic lung invasively, by advancing a treatment device into the lung and applying energy. Those invasive methods attempt to dilate the bronchi directly, rather than to stimulate nerve fibers that in turn bring about bronchodilation.

In contrast, the present invention discloses the use of noninvasive electrical stimulation of the vagus nerve (VNS) to dilate constricted bronchi. U.S. Pat. No. 6,198,970, entitled Method and apparatus for treating oropharyngeal respiratory and oral motor neuromuscular disorders with electrical stimulation, to FREED et al., describes noninvasive electrical stimulation methods for the treatment of asthma and COPD, but they involve direct stimulation of muscles instead of the vagus nerve. The present invention is unexpected because previous reports teach away from the use of (invasive or noninvasive) VNS to treat bronchoconstriction. Thus, in most subjects with asthma, vagal nerve activity contributes in varying degree to bronchoconstriction.

The vagus nerve innervates the heart, which raises additional concerns that even if VNS could be used to dilate bronchi, such vagus nerve stimulation could trigger cardiac or circulatory problems, including bradycardia, hypotension, and arrhythmia, particularly if the right vagus nerve is stimulated In fact, vasovagal

reactions are classically brought about by a triggering stimulus to the vagus nerve, resulting in simultaneous enhancement of parasympathetic nervous system (vagal) tone and withdrawal of sympathetic nervous system tone.

Accordingly, experiments show first that invasive electrical stimulation of the vagus nerve can in fact produce bronchodilation without first producing bronchoconstriction The success of those and subsequent experiments motivated the present disclosure that noninvasive methods and devices can also produce bronchodilation in humans, provided that the disclosed special devices and stimulation methods are used. Those devices and methods address not only the problems of producing bronchodilation and avoiding the production of abnormal heart rate or blood pressure, but also the problem of stimulating at the skin of the patient in such a way that a vagus nerve is selectively modulated, and in such a way that side effects including muscle twitching and stimulation pain are minimized or avoided.

Discussion

Once air is inhaled through the mouth or nose, it travels through the trachea and a progressively bifurcating system of bronchi (containing cartilage) and bronchioles (which contain little or no cartilage), until it finally reaches the alveoli, where the gas exchange of carbon dioxide and oxygen takes place. Through constriction or relaxation of smooth muscle within their walls, the bronchioles change diameter to either reduce or increase air flow. The bronchioles between the fourth and eighth bifurcation are thought to be most important in that regard. Normally, an increase in diameter (bronchodilation) to increase air flow is stimulated by circulating epinephrine (adrenaline) or sympathetic nerve fibers or so-called iNANC nerve fibers, and a decrease in diameter (bronchoconstriction) is stimulated by parasympathetic cholinergic nerve fibers, histamine, cold air, and chemical irritants. Reflexes have evolved to regulate the caliber of bronchioles, in which afferent nerves send state-dependent sensory signals to the central nervous system, which in turn sends efferent controlling signals back to the bronchi and bronchioles, thereby allowing smooth muscle (and other components) in the bronchi to adapt their caliber as needed to respond to such things as exercise, air-borne irritants, and infectious agents.

The present invention imparts non-invasive devices and methods for treating abnormal bronchial constriction, by stimulating selected nerve fibers that are responsible for reducing the magnitude of constriction of smooth bronchial muscle, such that the activity of those selected nerve fibers is increased and smooth bronchial muscle is dilated. In particular, the present invention provides methods and devices for immediate relief of acute symptoms associated with bronchial

constriction such as asthma attacks, COPD exacerbations, anaphylactic reactions, exercise-induced bronchospasm, and post-operative bronchospasm. The stimulated nerve fibers are particularly those associated with a vagus nerve (tenth cranial nerve).

In a preferred embodiment, electrodes applied to the skin of the patient generate currents within the tissue of the patient. An objective of the invention is to produce and apply electrical impulses that interact with the signals of one or more nerves to achieve the therapeutic result of bronchodilation. Much of the disclosure will be directed specifically to treatment of a patient by stimulation in or around a vagus nerve, with devices positioned non-invasively on or near a patient's neck. In particular, the present invention can be used to directly or indirectly stimulate or otherwise modulate nerves that innervate bronchial smooth muscle. However, it will be appreciated that the devices and methods of the present invention can be applied to other tissues and nerves of the body, including but not limited to other parasympathetic nerves, sympathetic nerves, spinal or cranial nerves.

The methods described herein of applying an impulse of energy to a selected region of a vagus nerve may be refined to propagate signals directly, or indirectly via the central nervous system, to at least one of the anterior bronchial branches of a vagus nerve, or alternatively to at least one of the posterior bronchial branches thereof. Preferably the propagated impulse is provided to at least one of the anterior pulmonary or posterior pulmonary plexuses aligned along the exterior of the lung. As necessary, the impulse may be directed to nerves innervating only the bronchial tree and lung tissue itself. In addition, the impulse may be directed to a region of the vagus nerve to stimulate, block and/or modulate both the cardiac and bronchial vagal branches. As recognized by those having skill in the art, this embodiment should be carefully evaluated prior to use in patients known to have preexisting cardiac issues.

Physiological Mechanisms by which Vagus Nerve Stimulation May Bring about Bronchodilation

A vagus nerve is composed of motor and sensory fibers. The vagus nerve leaves the cranium and is contained in the same sheath of dura matter with the accessory nerve. The vagus nerve passes down the neck within the carotid sheath to the root of the neck. The branches of distribution of the vagus nerve include, among others, the superior cardiac, the inferior cardiac, the anterior bronchial and the posterior bronchial branches. On the right side, the vagus nerve descends by the trachea to the back of the root of the lung, where it spreads out in the posterior pulmonary plexus. On the left side, the vagus nerve enters the thorax, crosses the left side of

the arch of the aorta, and descends behind the root of the left lung, forming the posterior pulmonary plexus.

A vagus nerve in man consists of over 100,000 nerve fibers (axons), mostly organized into groups. The groups are contained within fascicles of varying sizes, which branch and converge along the nerve, and which are surrounded by perineurium, epineurium, and fibrotic connective tissue. Each fiber normally conducts electrical impulses only in one direction, which is defined to be the orthodromic direction, and which is opposite the antidromic direction. Besides efferent output fibers that convey signals to the various organs in the body from the central nervous system, the vagus nerve conveys sensory information about the state of the body's organs back to the central nervous system. Some 80-90% of the nerve fibers in the vagus nerve are afferent (sensory) nerves communicating the state of the viscera to the central nervous system.

The largest nerve fibers within a left or right vagus nerve are approximately 20 μm in diameter and are heavily myelinated, whereas only the smallest nerve fibers of less than about 1 μm in diameter are completely unmyelinated. When the distal part of a nerve is electrically stimulated, a compound action potential is recorded by an electrode located more proximally. A compound action potential contains several peaks or waves of activity that represent the summated response of multiple fibers having similar conduction velocities. The waves in a compound action potential represent different types of nerve fibers that are classified into corresponding functional categories, with approximate diameters as follows: A-alpha fibers (afferent or efferent fibers, 12-20 μm diameter), A-beta fibers (afferent or efferent fibers, 5-12 μm), A-gamma fibers (efferent fibers, 3-7 μm), A-delta fibers (afferent fibers, 2-5 μm), B fibers (1-3 μm) and C fibers (unmyelinated, 0.4-1.2 μm). The diameters of group A and group B fibers include the thickness of the myelin sheaths.

In mammals, two vagal components have evolved in the brainstem to regulate peripheral parasympathetic functions. The dorsal vagal complex (DVC), consisting of the dorsal motor nucleus (DMNX) and its connections, controls parasympathetic function primarily below the level of the diaphragm, while the ventral vagal complex (VVC), comprised of nucleus ambiguus and nucleus retrofacial, controls functions primarily above the diaphragm in organs such as the heart, thymus and lungs, as well as other glands and tissues of the neck and upper chest, and specialized muscles such as those of the esophageal complex.

The parasympathetic portion of the vagus innervates ganglionic neurons which are located in or adjacent to each target organ. The VVC appears only in mammals and is associated with positive as well as negative regulation of heart rate, bronchial constriction, bronchodilation, vocalization and contraction of the facial muscles in

relation to emotional states. Generally speaking, this portion of the vagus nerve regulates parasympathetic tone. The VVC inhibition is released (turned off) in states of alertness. This, in turn, causes cardiac vagal tone to decrease and airways to open, to support responses to environmental challenges.

The parasympathetic tone is balanced in part by sympathetic innervations, which generally speaking supplies signals tending to relax the bronchial muscles, so that over-constriction does not occur. Overall, airway smooth muscle tone is dependent on several factors, including parasympathetic input, inhibitory influence of circulating epinephrine, iNANC nerves and sympathetic innervations of the parasympathetic ganglia. Stimulation of certain nerve fibers of the vagus nerve (up-regulation of tone), such as occurs in asthma or COPD attacks or anaphylactic shock, results in airway constriction and a decrease in heart rate. In general, the pathology of severe asthma, COPD and anaphylaxis appear to be mediated by inflammatory cytokines that overwhelm receptors on the nerve cells and cause the cells to massively upregulate the parasympathetic tone.

The role of a vagus nerve in controlling the caliber of a bronchus or bronchiole lumen may be illustrated. The bronchus or bronchiole is tubular in shape, the air in the lumen is in contact with a layer of mucus. That layer comprises water and various macromolecular glycoproteins disposed in a gel/sol structure. It may also contain trapped inhaled particles and cells that participate in an immune response to inhaled viruses, bacteria and other antigens. The mucus is produced by cells in and near the epithelial layer that lines the inner surface of the airway. The epithelium of the larger airways comprises ciliated, basal, goblet, brush, and small-granule cells, among which the goblet cells are responsible for much of the mucus. Larger airways also contain glands that contain two secretory cell types: the serous and the mucous cell, secretions from which reach the lumen via a duct inserted through the epithelium . The epithelium of the distal airways consists mainly of ciliated and bronchiolar exocrine (Clara) cells, and the latter cells produce much of the mucus there. Transport of the mucus to the mouth is due to ciliary beating of ciliated cells of the epithelium and to airflow.

A basement membrane anchors the epithelium to loose connective tissue that lies beneath the membrane. The lamina propria is the layer of connective tissue that lies immediately beneath the epithelium, which together with the epithelium constitutes the mucosa (or mucous membrane). Cells that participate in host defense are present in the lamina propria, such as cells of the innate-and adaptive-immune systems, including macrophages, neutrophils, eosinophils, dendritic cells, mast cells, natural killer cells, and lymphocytes. Those immune cells, interacting with the epithelial cells , are responsible for much of the defensive properties of the airways.

Host defense and the airway epithelium: frontline responses that protect against bacterial invasion and pneumonia.

Variable amounts of elastin may also be present in the lamina propria , or the elastin may appear as a layer under a generally separated or discontinuous circumferential layer of smooth muscle. Contraction and relaxation of the smooth muscle modulates the diameter of the bronchiole and its lumen, which thereby modulates the flow of air between the trachea and the alveoli, where gas exchange occurs. Capillaries or other small blood vessels are also present in the lamina propria, and blood vessels (arteries and veins, e.g., venules) occupy the region of adventitia between the smooth muscle layer and the peripheral site of bronchiolar attachment to alveoli or other lung structure such as cartilage.

Afferent nerve fibers within the bronchi and bronchioles sense the status of the airways and send that information towards the central nervous system. The brainstem and other central nervous tissue in turn process and integrate that information, along with information sensed from other lung structures and other organs (e.g., respiratory muscles, vasculature, heart, etc.), then send control signals along efferent nerve fibers to modulate the activity of structures directly or indirectly within the bronchi and bronchioles. Those neuronally-modulated structures are primarily the smooth muscle and the secretion glands, but the blood vessels, the immune cells within the lamina propria, and cells within the epithelium may be modulated as well.

Although both the sympathetic and parasympathetic branches of the autonomic nervous system innervate the airways, the parasympathetic branch dominates, especially with respect to control of airway smooth muscle and secretions. Parasympathetic tone in the airways is regulated by reflex activity often initiated by activation of airway stretch receptors and polymodal nociceptors.

The afferent parasympathetic nerve fibers are typically subclassified as low threshold mechanosensors and nociceptive-like fibers (slow-conducting, capsaicin-sensitive bronchopulmonary C fibers). The low threshold mechanosensors can be further subclassified as slowly (SAR) and rapidly (RAR) adapting stretch receptors. Less populous receptor types, e.g., those that respond particularly to punctate mechanical stimulation or rapid changes in pH, also exist. SARs lie in close association with airway smooth muscle and respond to stretch of the airway wall. Some fire throughout the respiratory cycle and others burst in response to lung inflation, with progressive increases in discharge rate as a function of lung volume. RARs are found throughout the tracheobronchial tree, primarily in and under the epithelium and in close approximation to bronchial venules. They are exquisitely sensitive to mechanical stimuli and respond with a rapidly adapting

discharge to large and rapid lung inflations and deflations. RARs are also stimulated or sensitized by intraluminal chemical irritants, smoke, dust, and environmental toxins. Because of the latter properties they are also known as irritant receptors.

Bronchial C-fiber receptors, which are innervated by nonmyelinated vagal afferent fibers, lie in the walls of the conducting airways. Their endings extend into the space between epithelial cells or form a plexus immediately beneath the basement membrane. The nociceptive nerves are more responsive to chemical mediators than the stretch sensitive RAR and SAR fibers (e.g., nicotine, acids, histamine, serotonin, bradykinin, and other mediators of inflammation). The C fibers are often referred to as “polymodal” fibers, because they respond to a broad range of stimuli. Activation of sensory C fiber receptors in the airways mucosa sets up axon reflexes with release of sensory neuropeptides. These neuropeptides cause vasodilatation, possibly with edema and plasma exudation, submucosal gland secretion, structural and functional changes in the epithelium, and possibly airway smooth muscle contraction.

The majority of afferent parasympathetic innervation to the lower airways is carried by the vagus nerves). The vagal afferent nerve fibers arise from cell bodies located in the vagal sensory ganglia. These ganglia take the form of swellings found in the cervical aspect of the vagus nerve just caudal to the skull. There are two such ganglia, termed the inferior and superior vagal ganglia. They are also called the nodose and jugular ganglia, respectively). The jugular (superior) ganglion is a small ganglion on the vagus nerve just as it passes through the jugular foramen at the base of the skull. The nodose (inferior) ganglion is a ganglion on the vagus nerve located in the height of the transverse process of the first cervical vertebra.

Terminations of each group of fibers (SAR, RAR, and C) are found in largely non-overlapping regions of the nucleus of the solitary tract. Second order neurons in the pathways from these receptors innervate neurons located in respiratory-related regions of the medulla, pons, and spinal cord. Those pathways control not only the bronchiole structures, but also the rate and depth of respiration and cardiopulmonary activity more generally.

Both afferent and efferent parasympathetic fibers traverse or skirt the nodose and jugular ganglia. With regard to the efferent parasympathetic fibers, which send control signals back to the bronchioles, preganglionic motor fibers (ganglionic branches) from the dorsal motor nucleus of the vagus and the special visceral efferents from the nucleus ambiguus descend to the nodose (inferior) vagal ganglion and form a band that skirts the ganglion. Thus, signals that are processed in the nucleus of the solitary tract (NTS) are sent to airway-related vagal

preganglionic neurons (AVPNs), located in the most rostral parts of the dorsal vagal nucleus and in the rostral nucleus ambiguus. From these preganglionic neurons, cholinergic outflow is sent via descending efferent intramural parasympathetic ganglia and then to tracheobronchial effector systems. In particular, postganglionic efferent cholinergic fibers profusely innervate the smooth muscle and the submucosal glands. In humans, there is comparatively little innervation of the airway epithelium , airway blood vessels, or lamina propria. Because the lamina propria is poorly innervated by efferent parasympathetic nerves in humans, cells of inflammatory and immune systems that are contained therein, such as macrophages, may receive little direct control there from those efferent nerves, although such control may be more significant in non-human species

The acetylcholine that is released from the preganglionic and postganglionic nerve fibers acts on target cell membranes through muscarinic receptors, including M2 and M3. The M3 receptors are found on bronchial airway smooth muscle and submucosal glands, causing smooth muscle contraction and secretion, when activated. Thus, contraction of airway smooth muscle is mediated by acetylcholine-induced activation of M3 receptors, which couple to the heterotrimeric G protein Gq/11, resulting in stimulation of phospholipase C and an increase in intracellular calcium. M3 receptors are also possibly found on endothelial cells and vascular smooth muscle. M2 receptors are also found on airway smooth muscle and submucosal glands. However, M2 activation by acetylcholine does not cause smooth muscle contraction, but instead antagonizes smooth muscle relaxation that is induced by beta-adrenoceptors. Thus, activation of M2 receptors inhibits the generation and accumulation of cyclic adenosine monophosphate (cAMP), thereby preventing bronchodilation. Other mechanisms may also modulate the contraction of the smooth muscle cells. For example, histamine that is released from activated mast cells may also cause bronchoconstriction. This is because H1-receptors are located in human bronchial muscle and are linked to transduction systems that cause increased intracellular Ca2+, which leads to muscle contraction.

The M2 receptors also play a significant role in the endings of the nerve fibers that transmit acetylcholine across the neuromuscular junction. M2 receptors in those fibers self-limit the transmission of acetylcholine, i.e., some of the transmitted acetylcholine activates those M2 receptors so as to then inhibit that same transmission. When this feedback inhibition becomes dysfunctional, excessive acetylcholine is transmitted to the smooth muscle, leading to hyper-responsiveness to allergens and excessive bronchoconstriction. Allergen-induced M2 receptor dysfunction is dependent upon selective recruitment of eosinophils to the airway nerves. Activated eosinophils release major basic protein, which binds to M2

receptors and prevents binding of acetylcholine. The binding of a virus may also affect the structure of the M2 receptor itself, or viruses may act via activation of inflammatory cells, in particular macrophages and T lymphocytes, leading to similar changes in receptor function that bring about similar dysfunction.

Noncholinergic parasympathetic nerves also innervate the airways. Noncholinergic parasympathetic transmitters are not co-released with acetylcholine from a single population of postganglionic parasympathetic nerves. Instead, an anatomically and functionally distinct parasympathetic pathway regulates nonadrenergic, noncholinergic relaxations of airway smooth muscle. The preganglionic nerves innervating airway noncholinergic, parasympathetic ganglia may be unmyelinated and may originate from a distinct location in nucleus ambiguus or may be derived from the dorsal motor nuclei of the vagus nerves. Unlike cholinergic contractions of the airway smooth muscle, which can reach a near maximum within about 30 seconds and can nearly completely reverse at the same rate, noncholinergic parasympathetic nerve-mediated relaxations are both slow in onset and reversal, requiring several minutes to reach equilibrium.

Noncholinergic parasympathetic neurotransmitters include the vasoactive intestinal peptide (VIP), the peptide pituitary adenylate cyclase-activating peptide (PACAP), peptide histidine-isoleucine, peptide histidine-methionine, and nitric oxide (NO). Fibers with those neurotramsmitters are primarily under parasympathetic control, although sympathetic nerves in the airways have also been shown to include such fibers. Both VIP and NO synthase have been localized to nerve fibers innervating airway smooth muscle and to parasympathetic ganglia in the airways. Because such non-adrenergic, non-cholinergic nerve fibers inhibit activities such as smooth muscle contraction, they are known as iNANC fibers. Excitatory non-adrenergic, non-cholinergic (eNANC) nerve fibers also exist. Responses to those fibers are mediated by the release of tachykinins such as substance P. In the presence of muscarinic blockade, vagal stimulation causes dilatation of preconstricted airways via noncholinergic neurotransmitters, demonstrating the dominance or overabundance of iNANC fibers relative to eNANC fibers.

It should be noted that a number of nonbronchiolar afferent nerve subtypes may also induce a withdrawal of cholinergic tone, including baroreceptors, skeletal muscle and diaphragmatic afferents, and pulmonary stretch receptors, some of which are also conveyed by the vagus nerve. These disparate afferent inputs may be simultaneously recruited, for example, during exercise. It should also be noted that although shows a reflex loop involving afferent and efferent nerve fibers sending signals from and to a single bronchiole, in reality signals from the afferent fibers emanating from one bronchiole may result in efferent signals that are sent to another bronchiole. This is particularly important as it relates to the cooperative

behavior of smooth muscle throughout the airways, as described later in connection with avalanches of bronchoconstriction and bronchodilation.

Turning now to control of the airways by the sympathetic nervous system, it is known that some sympathetic pulmonary afferent nerves exist. However, unlike the well-characterized parasympathetic afferent nerve fibers described above, the sympathetic afferent fibers have been described only as capsaicin-sensitive, substance P-containing spinal afferent neurons in the upper thoracic (T1-T4) dorsal root ganglia (DRG) that innervate the airways and lung.

With regard to the efferent sympathetic nerves, human airway smooth muscle is largely devoid of sympathetic adrenergic efferent innervation (in contrast to some other mammals), with relatively few fibers reaching the level of secondary bronchi and terminal bronchioles. Nevertheless, some sympathetic fibers do innervate the glands, vasculature, and parasympathetic ganglia of the human bronchial tree. Furthermore, recent evidence has suggested asthma patients do have such sympathetic innervations within the bronchial smooth muscle. Alpha-adrenergic receptors are localized on pulmonary and bronchial blood vessels, bronchial epithelial cells, submucosal glands, in parasympathetic ganglia, and on cholinergic and C afferent nerve fibers, where limited sympathetic innervation may occur. Beta-adrenergic receptors are numerous on airway smooth muscle, despite a lack of significant sympathetic innervation there, the significance of which is that beta-adrenergic control may be via circulating catecholamines rather than by the release of neurotransmitters from local nerve fibers.

In fact, the most significant parts of the sympathetic nervous system in regard to control of the airways may be within the parasympathetic ganglia and in the adrenal medulla. Postganglionic sympathetic nerve fibers intermingle with cholinergic nerves in parasympathetic ganglia, where sympathetic fibers may modulate cholinergic neurotransmission.

Fibers emanating from sympathetic ganglia that impinge upon the parasympathetic ganglia. Some of those fibers may terminate in the parasympathetic ganglia to modulate the parasympathetic fibers that reach the bronchi, and a small number of the sympathetic fibers may actually pass through or near the parasympathetic ganglia to reach the bronchi.

Epinephrine acts as a circulating hormone to participate in the regulation of bronchomotor tone through the stimulation of beta-2 receptors. Beta-adrenergic receptors are numerous on airway smooth muscle, and their stimulation by circulating catecholamines produces bronchodilatation. Epinephrine is derived mostly from the adrenal medulla, which is under the control of the sympathetic nervous system). The cells of the adrenal medulla are innervated directly by fibers

from intermediolateral nucleus (IML, in the thoracic spinal cord from T5-T11). Because it is innervated by preganglionic nerve fibers, the adrenal medulla can be considered to be a specialized sympathetic ganglion. It is ordinarily only during strenuous exercise that epinephrine concentrations are raised sufficiently to cause significant bronchodilation, e.g., to counteract bronchospasm that is induced by exercise in asthma. Repeated stimulation of some vagus nerve fibers may cause the repeated pulsatile systemic release of epinephrine (and/or other catecholamines), leading eventually to circulating steady state concentrations of catecholamines that are determined by the stimulation frequency as well as the half-life of circulating catecholamines.

The preceding paragraphs describe the efferent and afferent nerve fibers that respectively send signals to and from the bronchi and bronchioles. The paragraphs that follow describe the processing of the afferent sensory signals within the central nervous system to produce the efferent controlling signals. The neurons of this central respiratory network drive two functionally and anatomically distinct pools of motoneurons. Both groups have to be precisely coordinated to ensure efficient ventilation. One set, located within the spinal cord, innervates the diaphragm and intercostal muscles that force air into the lungs. A second group of motoneurons, with which this discussion is primarily concerned, is located within the nucleus ambiguus and to a lesser extent within the dorsal motor nucleus of the vagus. The latter group projects via the vagus nerve to coordinate the activity of laryngeal and bronchial muscle so as to control airway resistance and airflow.

The relevant interconnected centers are located in the medulla (nucleus tractus solitarius, nucleus ambiguus and dorsal motor nucleus of the vagus, rostral ventral lateral medulla, rostral ventral medial medulla, medullary raphe nuclei), the pons/midbrain (periaqueductal gray, locus ceruleus, raphe nuclei-e.g. dorsal), the diencephalon (hypothalamic nuclei, particularly the paraventricular nucleus of the hypothalamus), and the telencephalon (amygdala and its connections to the brain cortex). These same centers are involved more generally in the integration of cardiopulmonary functions and the regulation of body fluids (e.g., baroreflex and pH or CO2 chemoreception reflexes) \

Consider first the input to the central pathways. Vagal afferents traverse the brainstem in the solitary tract, with some eighty percent of the terminating synapses being located in the nucleus of the tractus solitarius (NTS). The NTS projects to a wide variety of structures, , including the amygdala, raphe nuclei, periaqueductal gray, nucleus ambiguus and the hypothalamus. The NTS also projects to the parabrachial nucleus, which in turn projects to the hypothalamus, the thalamus, the amygdala, the anterior insular, and infralimbic cortex, lateral prefrontal cortex, and other cortical regions.

A subset of NTS neurons receiving afferent input from SARs (termed pump or P-cells) mediates the Breuer-Hering reflexes and inhibits neurons receiving afferent input from RARs. Those reflexes are related to the control of spontaneous breathing rate and depth, especially in children and exercising adults, and they are also related to respiratory sinus arrhythmia, in which the heart rate is modulated by the respiratory rate and depth.

P-cells and second order neurons in the RAR pathway provide inputs to regions of the ventrolateral medulla involved in control of respiratory motor pattern. The core circuit components that constitute the neural machinery for generating respiratory rhythm and shaping inspiratory and expiratory motor patterns are distributed among three adjacent structural compartments in the ventrolateral medulla: the Bötzinger complex, pre-Bötzinger complex and rostral ventral respiratory group.

Axon collaterals from both P-cells and RAR interneurons, and likely from NTS interneurons in the C-fiber pathway, project to the parabrachial pontine region where they may contribute to plasticity in respiratory control, as well as integration of respiratory control with other systems, including those that provide for voluntary control of breathing, sleep-wake behavior, and emotions.

Consider now the output from the central pathways. Airway-related vagal preganglionic neurons (AVPNs) are the final common pathway from the central nervous system to the airways and transmit signals to the intrinsic bronchial ganglia that are part of the network for automatic feedback control. In most mammals, the motor preganglionic component of the network innervating the airways arises mainly from the nucleus ambiguus and to a lesser extent from the dorsal motor nucleus of the vagus (DMV). Of these two groups of neurons, AVPNs within the rostral nucleus ambiguus play a greater role in generating cholinergic outflow to airway smooth muscle.

Acetylcholine release at the bronchial smooth muscle is triggered by the activation of AVPNs, resulting in bronchoconstriction. Such activation of AVPNs is typically triggered by vagal C fibers via the activation of the NTS, wherein glutamate is released into the AVPNs. This C fiber activation may be in response to irritants, allergens, trauma, or idiopathic mechanisms associated with hypersensitivity. The activation may also be via A-delta fibers whose cell bodies reside in the jugular ganglia, which (like the C fibers) resemble the nociceptive fibers of the somatosensory system in that they have relatively high thresholds to mechanical stimuli and respond to classic nociceptive fiber-selective stimuli such as capsaicin and bradykinin.

Thus, the simplest feedback loop is one in which signals from afferent fibers to the NTS result in subsequent direct activation of the AVPNs by the NTS, resulting in a

level of broncho-constriction that is a function of the magnitude of the C or jugular A-delta fiber activation. It is understood that this level of constriction is largely a balance between the effects of cholinergic stimulation, iNANC relaxation, and relaxation due to circulating catecholamines. Mechanistically, the preganglionic nerves innervating airway noncholinergic, parasympathetic ganglia may originate from a distinct location in nucleus ambiguus or may be derived from the dorsal motor nuclei of the vagus nerves (dmnX).

However, AVPNs receive connections from multiple sites within the brain, not just the NTS, and these additional connections may inhibit glutamate-mediated activation of the AVPNs. Such additional connections have been demonstrated by retrograde transneuronal labeling with pseudorabies virus in C8 cord-transected rats. They include connections of the AVPNs to the amygdala, hypothalamus, periaqueductal grey matter of the midbrain (PAG), locus ceruleus, and raphe nuclei

Thus, the response of the AVPNs to excitatory inputs also depends on the inhibitory inflow to the AVPNs. Many inhibitory cell groups projecting to the AVPNs are linked to the hypothalamus, and a function of those projections is related in part to the control of respiration during sleep, maintenance of attention, motivation, and arousal states. When activated, GABA- and galaninergic cells inhibit histamine-containing neurons of the tuberomammillary nucleus (TMN) and the orexin-producing cells of the lateral hypothalamic area (LHA). This inhibition causes withdrawal of excitatory inputs from TMN and LHA neurons to serotonin (5-HT) expressing cells of raphe nuclei (RN) and the locus coeruleus (LC) norepinephrine-synthesizing cells. In addition, activation of neurons within the ventrolateral preoptic area directly inhibits LC and RN neurons, as well as GABA-containing cells of the ventrolateral periaqueductal gray (PAG), which project to AVPNs. Stimulation of the LC noradrenergic cell group and activation of parabrachial nucleus is known induce centrally mediated airway smooth muscle relaxation.

Thus, acting in opposition to glutamate-mediated (and possibly substance P) activation of the AVPNs by the NTS are GABA, and/or serotonin, and/or norepinephrine from the periaqueductal gray, raphe nuclei, and locus coeruleus, respectively. control of the inhibitory influence by the PAC, LC, and RN on the AVPNs may be exerted directly at sites within the nucleus ambiguus or dorsal motor nucleus. The inhibitory influence may also be on the nucleus tractus solitarius (NTS), which is connected bidirectionally to these centers. Thus, the inhibition may decrease the activation of the AVPNs by the NTS rather than simply inhibiting an already-existing activation of the AVPNs by the NTS. Alternatively, the inhibitory influence on the NTS may occur indirectly via the

hypothalamus owing to bidirectional connections between the NTS and hypothalamus.

The activation of inhibitory circuits in the periaqueductal gray, raphe nuclei, and locus coeruleus by the hypothalamus or NTS may also cause circuits connecting each of these structures to modulate one another. Thus, the periaqueductal gray communicates with the raphe nuclei and with the locus coeruleus, and the locus coeruleus communicates with the raphe nuclei,

Another structure also has a significant influence on AVPN activity, namely, the amygdala. The prefrontal cortex innervates the amygdala, which projects to multiple targets regulating autonomic functions, including the PAG, the NTS, and the nucleus ambiguus. Projections from the amygdala to the PAG are significant because the PAG neurons coordinate functions of multiple visceral organs involved in responses to stress, including those involving the airway. The effects of amygdala activity transmitted via the PAG to the AVPNs may be inhibitory or stimulatory, depending upon whether the patient is experiencing active or passive coping responses. such control of AVPN activity via the amygdala may be modulated by connections to the NTS, either directly or via the hypothalamus.

Finally, consider central modulation of the airways via the sympathetic nervous system. Only a limited number of discrete regions within the supraspinal central nervous system project to sympathetic preganglionic neurons in the intermediolateral column. The most important of these regions are the rostral ventral lateral medulla (RVLM), the rostral ventromedial medulla (RVMM), the midline raphe, the paraventricular nucleus (PVN) of the hypothalamus, the medullocervical caudal pressor area (mCPA), and the A5 cell group of the pons.

The rostral ventral lateral medulla (RVLM) is the primary regulator of the sympathetic nervous system, sending excitatory fibers (glutamatergic) to the sympathetic preganglionic neurons located in the intermediolateral nucleus of the spinal cord. Afferents affecting cardiopulmonary function synapse in the NTS, and their projections reach the RVLM via the caudal ventrolateral medulla. However, resting sympathetic tone also comes from sources above the pons, from hypothalamic nuclei, various hindbrain and midbrain structures, as well as the forebrain and cerebellum, which synapse in the RVLM.

The RVLM shares its role as a primary regulator of the sympathetic nervous system with the rostral ventromedial medulla (RVMM) and medullary raphe. Differences in function between the RVLM versus RVMM/medullary raphe have been elucidated in the case of cardiovascular control. In that case, barosensitive sympathetic efferents appear to be regulated primarily through the RVLM, whereas the cutaneous circulation is regulated predominantly through the RVMM and

medullary raphe. In the case of respiratory control, less is known, although it is thought that nociceptive sympathetic efferents are regulated through the RVMM and serotonin-containing medullary raphe. Differential control of the RVLM by the hypothalamus may also occur via circulating hormones such as vasopressin. The RVMM contains at least three populations of nitric oxide synthase neurons that send axons to innervate functionally similar sites in the NTS and nucleus ambiguus. Circuits connecting the RVMM and RVLM may be secondary, via the NTS and hypothalamus.

Individual normal bronchioles actually undergo constant constriction and dilation, such that the diameters of their lumens may vary considerably over the course of even a few minutes. Normally, some bronchioles are constricting while others are dilating, but the time-varying heterogeneity of airway caliber throughout the lung is normally sufficient to bring air to all the alveoli, because any constricted bronchiole would reopen in a relatively short period of time. This oscillation of constriction and dilation of individual bronchioles throughout the lung leads to physiological fluctuations in airway resistance at the level of the whole lung.

Accordingly, the present invention considers bronchiole segments to be oscillators, in which a mathematical variable corresponding to each bronchiole segment represents the time-varying radius of a bronchiole lumen, relative to a value representing a time-averaged radius of that bronchiole. Because segments of the bronchial tree are fluctuating according to the invention, the oscillating branches collectively give rise to fluctuations in overall respiratory impedance. It is thought that an asthma attack (or other bronchoconstrictive exacerbation) may correspond to an avalanche of airway constrictions, in which the constriction in one bronchiole segment increases the likelihood that another bronchiole branch in the same tree structure of the lung will constrict. The mechanisms linking one bronchiole segment to another include: the shared airflow in the lumens that connect one bronchiole to another; and neural connections to multiple bronchioles. As a result of the interconnected bronchiole fluctuations, some initial heterogeneity of airway constriction within different regions of the lung, which might seem to be of little physiological consequence, may actually become amplified by avalanches of airway constrictions, such that eventually large heterogeneous regions of the lung become unavailable for normal respiration.

Models have been constructed to explain such heterogeneity and avalanches (of closure and of reopening), but they have been used only to assess the risk of an asthma attack, rather than to explain or predict the actual occurrence of an asthma attack. A model of lung dynamics that is disclosed towards the end of this application is intended to make such a prediction for use in a feedforward controller. It does so by making oscillation of any one bronchiole oscillator be a

function of the state of other bronchiole oscillators, as well as a function of external conditions such as the presence of inhaled irritants and the accumulated effects of electrical stimulation of a vagus nerve. In one aspect of the present invention, the stimulation of a vagus nerve randomizes (e.g., through the quasi-random stimulation of individual fibers within the vagus nerve) afferent neural signals sent to the central nervous system, thereby resetting the phase relations between bronchiole oscillators, and consequently allowing for an avalanche-type reopening of bronchioles within regions of the lung that had been poorly ventilated, or for an inhibition of an avalanche-type bronchiolar closing. Quasi-random stimulation of efferent fibers by VNS may also be involved in such avalanche-type reopening

A vagus nerve being electrically stimulated according to the present invention, would in general modulate the activity of both afferent and efferent vagal nerve fibers. The particular structures within the patient that will be affected by the stimulation depend upon the details of the stimulation protocol. As described below, depending on whether the stimulation voltage is high or low, the stimulation may either constrict or dilate bronchial smooth muscle. As taught below in this disclosure, particular electrical stimulation waveforms bring about the dilation of constricted bronchi and bronchioles and also produce a minimum of unwanted side effects. The absence or minimization of unwanted side effects is also made possible by the use of noninvasive electrical stimulation devices that are disclosed herein, which shape the electrical stimulation in such a way as avoid the stimulation of tissue near the vagus nerve that would cause pain, unwanted muscle twitching, or other unwanted non-selective effects. Thus, the method of vagal nerve stimulation that is disclosed below uses parameters (intensity, pulse-width, frequency, duty cycle, etc.) that selectively activate certain structures. The stimulation waveform parameters are different from those used to treat other diseases with vagus nerve stimulation, such as epilepsy.

Mention was made above of a phase-resetting mechanism, wherein stimulation of the vagus nerve blocks a bronchial-closing avalanche or promotes a reopening bronchial avalanche. In view of the foregoing discussion of ways in which the vagus nerve can affect the bronchi, a large number of additional physiological mechanisms can be envisaged, many of which are not mutually exclusive. Depending on the details of the stimulation waveform and stimulation devices, the vagal nerve stimulation may stimulate, block, or otherwise modulate particular types of nerve fibers within the vagus nerve (e.g., afferent vs. efferent, nerve fiber types A, B, and/or C, parasympathetic or sympathetic, etc.). The stimulation may generate action potentials that propagate in orthodromic or in antidromic directions. More particular mechanisms may also be envisaged. For example, parasympathetic efferent cholinergic fibers could be blocked directly, thereby

inhibiting bronchoconstriction. Such inhibition could involve muscarinic receptors M2 or M3 or both. As another example, the VNS could result in the stimulation of efferent iNANC nerve fibers that promote bronchodilation. Alternatively, small numbers of sympathetic efferent fibers could directly cause relaxation of bronchial smooth muscle, or fibers from sympathetic ganglia could stimulate parasympathetic ganglia, thereby indirectly stimulating iNANC fibers to cause relaxation of bronchial smooth muscle. Alternatively, fibers from sympathetic ganglia could inhibit parasympathetic ganglia, thereby inhibiting parasympathetic cholinergic fibers from constricting smooth muscle. Alternatively, norepinephrine outflow from the sympathetic-innervated pulmonary vasculature could promote bronchodilation, or fibers from the interomediolateral nucleus could stimulate the adrenal gland, producing circulating epinephrine that relaxes bronchial smooth muscle. Furthermore, stimulation of the vagus nerve could directly inhibit the activation of the AVPNs by the nucleus tractus solitarius (NTS). Alternatively, the inhibitory influence on the NTS may occur indirectly via activation of the hypothalamus, and/or amygdala and/or periaqueductal gray and/or locus coeruleus and/or raphe nuclei. Alternatively, the inhibition may be the combined result of inhibitory and excitatory influences within the AVPNs. According to this aspect of the invention, noninvasive VNS with the disclosed devices activates pathways causing release of norepinephrine, serotonin and/or GABA (inhibitory neurotransmitters) onto the AVPNs, thereby preventing or reducing the release of acetylcholine in the airways and resulting in bronchorelaxation. According to this view, noninvasive VNS acts as a central, specific, airway anticholinergic, but without any of the side effects of systemic anticholinergic therapy. In addition, these same inhibitory neurotransmitters act on the mucous glands throughout the airway passages in the nose, mouth, throat and lungs of the patient. Therefore, the noninvasive VNS taught by the present invention also serves to inhibit mucous production in these airway passages, resulting in increased airflow throughout these passages. Thus, the present invention can provide a dual benefit: (1) an immediate reduction in acetylcholine release to the lungs, providing an immediate (within minutes or seconds) bronchodilation effect for the patient; and (2) a decrease in mucous production which provides a more gradual improvement of airflow to the patient. The decrease in mucus production serves to reduce the mucociliary escalator clearance of the petitioned enhanced pulmonary drug delivery system.

Brief Summary of the Invention

The present invention involves devices and methods for the treatment of a variety of diseases and disorders that are primarily or at least partially driven by an imbalance in neurotransmitters in the brain, such as asthma, COPD, depression, anxiety, epilepsy, fibromyalgia, and the like. The invention involves the use of an

energy source comprising magnetic and/or electrical energy that is transmitted non-invasively to, or in close proximity to, a selected nerve to temporarily stimulate, block and/or modulate the signals in the selected nerve.

In one aspect of the invention, a method of treating a disorder comprises positioning a device adjacent to a skin surface of the patient, generating one or more electrical impulses with said device and transmitting the electrical impulses to a vagus nerve in the patient. The electrical impulses are sufficient to generate an electric field at the vagus nerve above a threshold for generating action potentials within fibers of the vagus nerve responsible for activating neural pathways causing release of inhibitory neurotransmitters within a brain of the patient. In a preferred embodiment, the inhibitory neurotransmitters are one or more of the following: GABA, serotonin and/or norepinephrine.

The applicant has discovered that many seemingly disparate disorders may, in fact, have common causes that manifest into different symptoms or disorders in different individuals. Specifically, the applicant has discovered that in certain individuals who may suffer from disorders, such as depression, asthma, COPD, migraine, cluster headache, anxiety, fibromyalgia, epilepsy and the like, certain areas of the brain are prone to periodic or continuous excessive excitatory neurotransmitter levels. These periodic excessive excitatory neurotransmitter levels can be caused by certain “triggers”, such as noxious substances entering the lungs that cause airway reactivity or other triggers, such as chocolate or seafood that can cause migraines in certain individuals. In other cases, the patient may have pathologically high excitatory neurotransmitter levels on a continuous basis without any particular trigger. One example, of an excitatory neurotransmitter is glutamate, which is known to be associated with migraines.

The excessive excitatory neurotransmitter levels in a patient's brain can be caused by inaccurate signals from the body transmitted through the vagus nerve or other nerves or these excessive levels can be caused by the brain overreacting to normal signals coming from the body. In some cases, these excessive excitatory neurotransmitter levels may be caused by inappropriate inactivity in the production and/or release of inhibitory neurotransmitters, such as GABA, serotonin and/or norepinephrine. A reduced level of these inhibitory neurotransmitter levels can result in excessive levels of the excitatory neurotransmitters that they are meant to balance.

The present invention seeks to address this imbalance in neurotransmitters in the brain that can result in many of the disorders mentioned above. Specifically, afferent nerve fibers in the vagus nerve are stimulated with the devices, signals and methods described above to heighten activity in areas of the brain (e.g., the periaqueductal gray, locus ceruleus and/or raphe nuclei) resulting in the release of

inhibitory neurotransmitter levels, such as GABA, norepinephrine and/or serotonin). For example, as discussed above, heightened activity in the locus coeruleus will result in a release of norepinephrine or an increase the release of norepinephrine. This release of inhibitory neurotransmitters suppresses the excessive excitatory neurotransmitters and creates balance in the brain such that the brain either does not overreact to certain stimuli and/or to modulate the pathologically high level of excitatory neurotransmitters.

Another of the key advantages with the present invention is that the electrical field is above the threshold for generating action potentials within A and B fibers of the vagus nerve but below the threshold for the C fibers. Thus, the A and B fibers are selectively stimulated without stimulating the C fibers of the vagus nerve. The method of the present invention allows for selective stimulation of nerves responsible for activating neural pathways that will cause the release of inhibitory neurotransmitters within the brain to treat a variety of disorders in a patient. At the same time, the stimulation has substantially no effect on heart rate or blood pressure and it will not cause bronchoconstriction.

In a preferred embodiment, the electric field at the vagus nerve is between about 10 to 600 V/m and more preferably less than 100 V/m. The electrical field gradient is preferably greater than 2 V/m/mm. The electrical impulses are substantially constrained from modulating the nerves between the outer skin surface of the patient and the vagus nerve. The electric field is preferably not sufficient to produce substantial movement of the skeletal muscles of the patient.

In one embodiment of the invention, the stimulator comprises a source of electrical power and two or more remote electrodes that are configured to stimulate a deep nerve relative to the nerve axis. In one embodiment, the stimulator comprises two electrodes that lie side-by-side within separate stimulator heads, wherein the electrodes are separated by electrically insulating material. Each electrode is in continuous contact with an electrically conducting medium that extends from the interface element of the stimulator to the electrode. The interface element also contacts the patient's skin when the device is in operation.

Current passing through an electrode may be about 0 to 40 mA, with voltage across the electrodes of about 0 to 30 volts. The current is passed through the electrodes in bursts of pulses. There may be 1 to 20 pulses per burst, preferably five pulses. Each pulse within a burst has a duration of about 20 to 1000 microseconds, preferably 200 microseconds. A burst followed by a silent inter-burst interval repeats at 1 to 5000 bursts per second (bps, similar to Hz), preferably at 15-50 bps, and even more preferably at 25 bps. The preferred shape of each pulse is a full sinusoidal wave.

A source of power supplies a pulse of electric charge to the electrodes or magnetic stimulator coil, such that the electrodes or magnetic stimulator produce an electric current and/or an electric field within the patient. The electrical or magnetic stimulator is configured to induce a peak pulse voltage sufficient to produce an electric field in the vicinity of a nerve such as a vagus nerve, to cause the nerve to depolarize and reach a threshold for action potential propagation. By way of example, the threshold electric field for stimulation of the nerve may be about 8 V/m at 1000 Hz. For example, the device may produce an electric field within the patient of about 10 to 600 V/m (preferably less than 100 V/m) and an electrical field gradient of greater than 2 V/m/mm. The electric fields produced by the present invention at the vagus nerve are generally sufficient to excite all myelinated A and B fibers, but not the unmyelinated C fibers. However, by using a reduced amplitude of stimulation, excitation of A-delta and B fibers may also be avoided.

The preferred stimulator shapes an elongated electric field of effect that can be oriented parallel to a long nerve, such as a vagus. By selecting a suitable waveform to stimulate the nerve, along with suitable parameters such as current, voltage, pulse width, pulses per burst, inter-burst interval, etc., the stimulator produces a correspondingly selective physiological response in an individual patient, such as bronchodilation. Such a suitable waveform and parameters are simultaneously selected to avoid substantially stimulating nerves and tissue other than the target nerve, particularly avoiding the stimulation of nerves that produce pain.

In one embodiment, the present invention is particularly useful for the acute relief of symptoms associated with bronchial constriction, e.g., asthma attacks, COPD exacerbations and/or anaphylactic reactions. The teachings of the present invention provide an emergency response to such acute symptoms, by producing an almost immediate airway dilation, enabling subsequent adjunctive measures (such as the administration of epinephrine) to be effectively employed. The invention may be useful for treating bronchoconstriction in patients who cannot tolerate the side effects of albuterol or other short acting β-agonists, who do not gain sufficient benefit from anticholinergic medications including tioproprium bromide, or whose airway resistance is too high to get adequate benefit from inhaled medications. In preferred embodiments, the disclosed methods and devices do not produce clinically significant side effects, such as changes in heart rate or blood pressure.

One aspect of the method includes stimulating, inhibiting, blocking or otherwise modulating nerves that directly or indirectly modulate parasympathetic ganglia transmission, by stimulation or inhibition of preganglionic to postganglionic transmissions. According to this feature of the invention, noninvasive vagus nerve stimulation with the disclosed devices can activate pathways causing release of

norepinephrine, serotonin and GABA (inhibitory neurotransmitters) onto airway-related vagal preganglionic neurons (AVPNs), thereby preventing release of acetylcholine in the airways, and resulting in bronchorelaxation. These neural pathways also innervate the mucous glands in the lungs and other airway passages. Thus, the activation of these neural pathways also inhibits mucous production in the airways, increasing airflow to and from the patient's lungs.

In yet another aspect of the present invention, the selected nerve fibers comprise those that send an afferent vagal signal to the brain, which then triggers an efferent sympathetic signal to stimulate the release of catecholamines (comprising endogenous beta-agonists, epinephrine and/or norepinephrine) from the adrenal glands and/or from nerve endings that are within the lung or distributed throughout the body.

The stimulating step is preferably carried out without substantially stimulating excitatory nerve fibers, such as parasympathetic cholinergic nerve fibers, that are responsible for increasing the magnitude of constriction of smooth muscle. In this manner, the activity of the nerve fibers responsible for bronchodilation are increased without increasing the activity of the cholinergic fibers, which would otherwise induce further constriction of the smooth muscle. Alternatively, the method may comprise the step of actually inhibiting or blocking these cholinergic nerve fibers such that the nerves responsible for bronchodilation are stimulated while the nerves responsible for bronchial constriction are inhibited or completely blocked. This blocking/inhibiting signal may be separately applied to the inhibitory nerves; or it may be part of the same signal that is applied to the nerve fibers directly responsible bronchodilation.

The method of treating bronchial constriction includes applying an energy impulse to a target region in the patient, preferably over a period of less than two minutes, and acutely reducing the magnitude of bronchial constriction in the patient. Preferably, the bronchodilation effect lasts from about 2 to 8 hours.

Part Two

The novel systems, devices and methods for treating disorders and providing an enhanced pulmonary drug delivery system inclusive of the section ‘Part Two’ are more completely described in the ‘Detailed Description of the Invention’, with reference to drawings to be provided, and in claims appended hereto. Other aspects, features, advantages, etc. will become apparent to one skilled in the art when the detailed description of the invention herein to be taken in conjunction with the forthcoming accompanying drawings.