# Are There Causal Relationships Between the Development of the Inflammatory Diseases Amyotrophic Lateral Sclerosis and Asthma?

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**Amyotrophic lateral sclerosis (ALS) and asthma are inflammatory diseases. ALS is a fatal progressive, neurodegenerative disease with inflammation around the upper and lower motor neurons leading to their degeneration, muscle atrophy, paralysis, and death. Asthma is a chronic inflammatory disease with reversible airway obstruction and nonspecific airway hyper-reactivity. The local release of sensory neuropeptides from capsaicin-sensitive primary afferents causes motor neuron pathophysiology and airway inflammation and hyper-reactivity. While there is no cure for ALS, asthma is managed according to its symptoms and severity, to decrease the symptoms, improve pulmonary function, and reduce morbidity. To determine whether understanding asthma may provide insights into how to clinically deal with ALS, the authors examined the etiologies of ALS and asthma, and the factors that exacerbate the symptoms. Although no direct correlations were found, the similar multifactorial triggers, and the critical roles of neuronal inflammation, suggest that one or more exists.**

*Key words: Neurodegeneration, Inflammation, Respiratory disease, Neuron death*

Inflammation in the brain is recognized to play an important role in the pathogenesis of several neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS), Parkinson's and Alzheimer's disease. Inflammation-mediated neuro-degeneration involves activation of the brain's resident immune cells, the microglia, which produce proinflammatory and neurotoxic factors, including cytokines, reactive oxygen intermediates, nitric oxide, and eicosanoids that induce neuro-degeneration. Hence, compounds that prevent microglial activation may act as therapeutic agents for inflammation-mediated neurodegenerative diseases.

ALS is a fatal paralytic progressive neurodegenerative disease characterized by inflammation surrounding upper and lower motor neurons, their selective degeneration and resulting in spasticity, diffuse muscular atrophy, weakness, paralysis of skeletal muscle, and ultimately death from respiratory failure. Currently there is no cure or effective treatment for ALS. ALS occurs with virtually identical prevalence throughout the world, regardless of climate or socioeconomic level.

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Asthma is a chronic inflammatory disease characterized by reversible airway obstruction, nonspecific airway hyper-reactivity, extensive neurogenic inflammatory responses involving local activation of in the inflammatory regions of neuropeptides which results in further neuron and inflammatory actions. Although there is no cure for asthma, its various treatments are aimed at decreasing symptoms and at preventing disease exacerbation. The incidence of asthma in the world is highest in the United States, and within that population, it is highest in Hispanics, of which Puerto Ricans have the highest prevalence (12).

The authors of this review knew a woman, borne and raised in Puerto Rico, who suffered life-time of serious challenges from chronic asthma and died from ALS at the age of 52. The development of asthma and ALS in this individual raised the questions of whether she suffered from similar triggers of asthma and ALS, or the physiological stresses of asthma could have led to the development of ALS.

Both ALS and asthma show distinct parallels in the significant involvement of inflammation surrounding neurons, which results in neuronal activation and toxicity. Although there are extensive epidemiological data on the occurrence of asthma and ALS, there are no data on their occurrence in the same individual. This review examines the etiology of asthma and ALS, as well as the manifestations of the diseases. Because both diseases involve extensive inflammatory challenges to neurons, we

looked for clues to whether there may be more than a casual correlation between the development of both diseases in an individual. Except for the remarkable parallels between both diseases, no direct or casual relationship could be found between the triggers of ALS and asthma.

## Etymology of ALS

The distribution of ALS worldwide can be described by three main groups: (1) sporadic; (2) familial; and (3) the Western Pacific variant.

## Sporadic ALS

Individuals who develop ALS, but who have no family member with the condition, are said to have sporadic or classical ALS. In the United States 90–95% of ALS cases are sporadic. Sporadic ALS appears to be increasing worldwide although the causes are not clear. Excessive levels of glutamate released from astrocytes can lead to neurotoxicity (8, 74). United States and other countries report annual incidence rate of 0.2 to 2.4 per 100,000 population and a prevalence of 0.8 to 7.3 per 100,000 population (22, 23). The onset of ALS is age-related with the highest rate of onset occurring between 55 and 75 years of age (22, 23, 37).Prognosis also appears to be age-related with slightly better survival occurring among those with a younger age at onset (3). ALS is more common in males than females by a ratio of 1.5 - 2 to 1 (22, 74), but recent studies have suggested that this sex difference is decreasing over time (22, 85).

Differences in the frequency of ALS by race/ethnicity have also been observed. Mortality data in the United States indicates that the disease is more common among whites compared to non-whites (78, 82). A study in Mexico suggested that ALS prevalence is lower than in other parts of the world (109). A subsequent investigation at a Mexico City referral clinic did not support these differences, and a mortality study in Harris County, Texas showed no significant difference in mortality rates between Hispanics and non-Hispanic whites (4, 110).

The genetic role in sporadic ALS is substantially higher than expected, estimated to account for 38 to 85 percent of the risk (48). However, many researchers believe that sporadic ALS may result from a combination of genetic and environmental factors (96).

## Familial ALS

Familial ALS is defined as two or more cases of ALS occurring in the same family. About five to ten percent of ALS cases are familial (102, 121, 122). Familial ALS is inherited as an autosomal dominant trait, meaning that a child of a parent with familial ALS has a 50% chance of inheriting the defective gene. Approximately 15 to 20% of all familial ALS cases are attributed to one of several mutations in the Cu/Zn superoxide dismutase (SOD) gene (28, 37, 122). Unlike sporadic ALS, familial ALS is distributed equally among men and women (98). Individuals with familial ALS also have a poorer prognosis than those with sporadic ALS, with a typical survival time of one to two years (98)

Risk factors for developing ALS include an inherited genetic defect, which accounts for 5–10% of cases of familial ALS (FALS) in the United States. FALS is linked to a genetic defect on chromosome 21 (44). This gene codes for an enzyme called superoxide dismutase (SOD), an antioxidant that protects motor neurons from free radical damage (i.e., molecules introduced to the body, or produced by body processes that interact and cause cellular damage) (120). More than 60 different mutations that cause SOD to lose its antioxidant properties have been found. However, only 20% of familial ALS cases are linked to SOD mutations, so there may be other unknown genetic defects involved (46).

## High Risk Foci in the Western Pacific

In certain areas of the Western Pacific, the incidence of ALS has been reported to be 50- to 150-fold higher than in other regions of the world (98). These high risk foci include Guam, the Kii Peninsula of Japan, and Western New Guinea. ALS patients in these areas often simultaneously acquire symptoms or pathological characteristics similar to Parkinson's disease and Alzheimer's disease. The ALS/Parkinson dementia complex (ALS/PDC) observed in these communities is clinically distinct from classical ALS. Patients who develop ALS/PDC are usually younger and live longer with the disease (mean age at onset 46 years, mean age at death 52 years for women and 50 years for men) (17). Over the past 40 years, the incidence of ALS/PCD in these high risk foci has decreased substantially to rates that are only slightly higher than other regions of the world (98). These dramatic changes in disease incidence suggest the influence of an environmental factor that has been altered over time. These foci have been investigated extensively in the hopes of identifying environmental risk factors that may account for the elevated risk among these populations.

For the population of Guam, it is suspected that a dietary neurotoxin is the risk factor for the development of Guamanian ALS. The suspected neurotoxin is an amino acid, a cyanobacterial origin of beta-methylaminoalanine (BMAA). BMAA is found in the seed of the cycad *Cyas cirinalis*, a tropical plant found in Guam, which was used to make flour and was a major dietary component during the 1950s and the early 1960s, when this type of ALS had an exceptionally high incidence (59, 99).

## ALS

Neuron death associated with ALS is ascribed to many different causes, including oxidative damage, loss of trophic factor support, glutamate-mediated excitoxicity, secondary chronic inflammation and caspase activation. Further, human neurons produce many inflammatory proteins and their inhibitors, creating complex interactions. Therefore, many different drugs have been tested in an attempt to counteract the different causes of neuron death. However, the pathogenesis of ALS is most likely the result of a complex interaction between multiple factors and thus, combinations of drugs will most likely be required to reduce or block the multifactorial neurodegeneration process.

Experimental animal models of ALS, such as the transgenic rodents, which express the mutant superoxide dimutase-1 (SOD), continue to play a pivotal role developing an understanding of ALS pathogenesis, and in testing of new therapeutic interventions aimed at protecting against neurodegeneration (51, 56).

Postmortem analysis of patients with several degenerative neurological diseases, including Alzheimer's and Parkinson's disease implicates the involvement of microglia in the neurodegenerative process (83). Activated microglia secrete a variety of proinflammatory and neurotoxic factors that are believed to induce and/or exacerbate neuro-degeneration (18, 140). However, it is not known whether microglial activation plays a role in the initiation stage of disease progression, or is a response to neuronal death.

Neuro-inflammation is a characteristic of pathologically affected tissue in several neurodegenerative disorders. These changes are seen in the brainstem and spinal cord of ALS cases and in mouse models of the disease. They include an accumulation of large numbers of activated microglia and astrocytes, as well as small numbers of T cells, mostly adhering to postcapillary venules (90, 92). Along with the biochemical alterations are the appearance of numerous molecules characteristic of free-radical attack, the occurrence of proteins associated with activation of the complement cascade, and a sharp up-regulation of the enzyme cyclooxygenase 2 (COX-2) (26, 95). Thus, anti-inflammatory agents may have a role to play in treating ALS, with COX-2 being a particularly attractive target because of its marked increase in ALS spinal cord of ALS patients (26).

## Environmental Factors and ALS

In a number of small communities around the United States (Illinois, Massachusetts, Texas and Washington) unusual elevated incidences of ALS have been noticed. In each case, the towns are located near hazardous wastes sites containing contaminates that scientific literature suggests may be associated with triggering ALS (as well as multiple sclerosis, MS). The hazardous waste contaminants of concern include heavy metals, trace elements, fuels, solvents and other volatile organic chemicals, radiation, and agricultural chemicals (12, 21, 43, 49, 77, 88, 93, 119, 123).

No consistent epidemiological clues concerning the cause of ALS have been found in epidemiological studies. However, other potential risk factors associated with increased death rates from ALS include infectious agents, smoking (in women but not men) (6, 41, 64, 139), nutritional intake (ALS patients have a chronically deficient intake of energy and should augment their energy intake rather than the consumption of high-protein nutritional supplements (66, 127), and the ingestion of neurotoxic seeds, fruits and plants (20), physical exertion (22).

## Asthma

Asthma is a chronic inflammatory disease characterized by reversible airway obstruction and nonspecific airway hyper-reactivity. Asthma is the most common chronic illness of childhood (68). The average incidence of asthma in most other countries is 6.4%, while the highest prevalence of childhood asthma in the world is in the United States at 11.1% (10.6% male / 11.6% female). Within the United States, the Hispanics suffers the highest prevalence of asthma 8.3% (8.1% males / 8.5% females), and within Hispanics the highest prevalence is among Puerto Ricans 20.3% (12), (19.5% male/ 21.0% female) (5, 68). Some triggers of asthma are allergen exposure (e.g. HDM, pet dander, pollens etc.) (39, 72, 143), smoking (81), exercise in cold-air which causes a drying of the airway mucosa (54, 84), drugs (such as Beta blockers, non-steroidal anti-inflammatory drugs and anaphylactoids , food additives (such as sulphites) (89, 133), and viral upper respiratory tract infections - especially rhinovirus (129, 135).

Asthma disproportionately burdens many socio-economically disadvantaged urban communities, and is associated with socioeconomic status and certain ethnic makeup (47). Manifestation of environmental factors include housing conditions, hygiene, indoor environmental exposures including allergens, traffic air pollution, disparities in treatment and access to care, and cigarette smoking. Also involved are environmental influences on somatic growth, such as low birth weight, prematurity, and obesity. The environmental component is clearly indicated by the finding that the rate of asthma is higher among U.S.-born than Mexican-born Mexican Americans (57). This finding highlights the importance of environmental exposures in developing asthma in a migratory population.

The allergic early-phase reaction, a hallmark of allergic bronchial asthma, is caused by allergen and immunoglobulin E-dependent mediator release from mast cells (126). The local release of sensory neuropeptides from capsaicin-sensitive primary afferents elicits prominent motor and inflammatory actions in mammalian airways (35, 138). This neurogenic inflammation can contribute to the pathophysiology of asthma and airway hyperreactivity (87).

Asthma is managed in steps according to disease symptoms and severity. Treatment goals are to decrease symptoms, improve pulmonary function, and reduce overall morbidity and the associated cost of medical care. Anti-asthma drugs are a key component of asthma management and are classified as either long-term-control medications that control symptoms and prevent disease exacerbations, or quick-relief medications that rapidly relieve airway obstruction and acute asthma symptoms. Several new leukotriene (LT) modulators (competitive and selective leukotriene receptor antagonists) provide prophylaxis and treatment of chronic asthma including the LT receptor antagonists montelukast, zafirlukast and the 5-lipoxygenase inhibitor zileuton (15, 79, 80). Each decreases symptoms and the use of rescue medication, and improves pulmonary function in patients with mild intermittent to moderate persistent asthma (1, 69, 70).

## Commonality of ALS and asthma

### The immune system.

There is extensive evidence that neurons and immune cells communicate, and that these interactions are involved in the lung inflammation of asthmatic patients (117, 118). Neurotrophins appear to be responsible for regulating and controlling the crosstalk between the immune and peripheral nervous systems. They are constitutively expressed by resident lung cells and are produced in increasing concentrations by immune cells that invade the airways under pathological conditions. Neurotrophins modify the functional activity of sensory and motor neurons, leading to enhanced and altered neuropeptide and tachykinin production, with the consequence of the development of neurogenic inflammation.

Target and effector cells responsible for airway hyper-responsiveness and airway obstruction include sensory and motor neurons, as well as epithelial and smooth muscle cells. Although it is well established that the inflammatory process is controlled by T-helper-2 (Th2) cells of the immune system, the mechanisms by which immune cells interact with neurons, epithelial cells or smooth muscle cells still remain uncertain.

Airway neurogenic inflammation is caused by tachykinins released from sensory neuron peripheral nerve endings within the airways, and is characterized by plasma protein extravasation, airway smooth muscle contraction and increased secretion of mucus (25, 108). Tachykinins are degraded and inactivated by neutral endopeptidase (NEP), a membrane-bound metallopeptidase, which is located mainly at the surface of airway epithelial cells, but is also present in airway smooth muscle cells, submucosal gland cells and fibroblasts (62, 128). The key role of NEP in limiting and regulating the neurogenic inflammation provoked by different stimuli has been demonstrated in a large series of studies published in recent years. It has also been shown that a variety of factors, which are relevant for airway diseases, including viral infections, allergen exposure, inhalation of cigarette smoke and other respiratory irritants, is able to reduce NEP activity, thus enhancing the effects of tachykinins within the airways (34). On the basis of these observations, the reduction of neutral endopeptidase activity appears to be a factor that switches neurogenic airway responses from their physiological and protective functions to a detrimental role that increases and perpetuates airway inflammation (34).

The immune system plays a role in the pathogenesis of ALS. The majority of the many diffusely scattered lymphocytes seen in the anterior and lateral corticospinal tracts and anterior horns belong to the suppressor/cytotoxicity T-cell subset and are mixed with macrophages (130). Helper-inducer T-cells are rare and B-cells are conspicuously absent. Compared to controls, ALS specimens exhibit an increase in major histocompatibility complex (MHC) products or human leukocyte antigens (HLA) in the corticospinal tracts and anterior horns. HLA-ABC antigens are expressed in the honeycomb pattern of the glial matrix of the spinal cord, and HLA-DR antigens are strongly expressed by large dendritic cells. In addition, macrophages and endothelial cells are labeled by HLA-DR. These findings suggest that an autoimmune process, or an infectious agent, play a role in ALS.

### Inflammation

Inflammatory mechanisms play a major role in the pathogenesis of ALS in humans, and in transgenic mouse models. Inflammation in ALS spinal cord and cortex is due to the innate immune responses by macrophages and mast cells and adaptive immune responses by T cells. However, it is unclear if the disease is propagated through inflammation, or whether in contrast, evidence of inflammation reflects an attempt to protect against further cellular injury.

Naturally occurring sexual dimorphism is implicated in the risk, progression and recovery from numerous neurological disorders, such as head injury, multiple

sclerosis (MS), stroke, and neurodegenerative diseases: Parkinson's disease (PD), Alzheimer's disease (AD) or ALS. Evidence suggests that the observed differences in incidence between men and women result from estrogen's wide range of effects within the mammalian central nervous system (CNS), with its neuroprotective effect being one of the most important. The anti-inflammatory activity of estrogen may be responsible for its neuroprotective role (3, 19).

MS patients and mice subjected to experimental autoimmune encephalomyelitis (EAE) display gender specific alterations of IFN-gamma and IL-12, variations of TNF and IL-6 associated with PD (29). Thus, hormonal anti-inflammatory treatment may be one pathway to limit the damages caused by neurodegenerative diseases.

Inflammatory pathways involving the cyclooxygenase (COX) enzymes and subsequent generation of prostaglandins are potential target sites for treatments to halt the progression of ALS (26). In the CNS, COX enzymes are localized to neurons, astrocytes, and microglia and can be induced under various conditions.

Inhibition of a key mediator of inflammation, COX-2, represents a promising therapeutic approach in ALS (7). The specific COX-2 inhibitor Rofecoxib brings about a small delay in the onset of locomotor impairment in the mouse model of the familial form of ALS (fALS) (7).

Macrophages in the spinal cord of ALS patients show both strong expression of COX-2 (one log greater than control tissues) and inducible nitric oxide synthase (50). In the gray matter, these macrophages surround dying neurons and appear to phagocytize them (NeuN-positive) (50).

## Neurogenic activation: Neurotransmitters and Neurotrophic Factors

### Neurotransmitters

Although asthma is considered an inflammatory disease of the airways, neural mechanisms are also very important. In addition to the classic neural pathways, the non-adrenergic, non-cholinergic pathway has been described in the airways of animals and humans. Neural control of the airways may be abnormal in asthma and neurogenic mechanisms may contribute to the pathophysiology of asthma.

Sensory, parasympathetic, and sympathetic neurons in airways contain neuropeptides, which induce have proinflammatory effects, such as increased mucus production, micro-vascular leakage, and smooth muscle contraction (24). Neuropeptides released from sensory nerves (i.e. neurokinin A and substance P) mediate excitatory non-adrenergic, non-cholinergic transmission, which cause broncho-constriction and bronchial hyper-responsiveness.

Inhibitory non-adrenergic and non-cholinergic (i-NANC) nerves are the only bronchodilator pathway in human airways, and their neurotransmitter is predominantly nitric oxide, although vasoactive intestinal peptide may be contributory (11, 63). It is possible that i-NANC function may be abnormal in asthma as a consequence of inflammation. Unmyelinated sensory nerves contain a variety of potent inflammatory peptides, including substance P and neurokinin A, which might be released in chronic inflammation, particularly if there is a proliferation of these nerves, increased neuropeptide synthesis or reduced metabolism by neutral endopeptidase (9).

The local release of sensory neuropeptides from capsaicin-sensitive primary afferents elicits prominent motor and inflammatory actions in mammalian airways. This neurogenic inflammation can contribute to the pathophysiology of asthma and airway hyperreactivity. In this review evidence will be presented regarding the involvement of this peptidergic neural pathway in the mediation of some pulmonary actions of lipid mediators such as eicosanoids and PAF (87).

Cholinergic nerves are the predominant bronchoconstrictor pathway in airways and cholinergic neurotransmission may be increased in asthma by the effects of inflammatory mediators on afferent nerves (reflex effect) and on prejunctional receptors on postganglionic nerves (9). In addition, there may be a defect in prejunctional M2-receptors on cholinergic nerves resulting in increased cholinergic neural effects, and beta-adrenoceptor function may be abnormal in asthmatic airways due to chronic inflammation (27, 53). But alpha-receptors are probably unimportant in regulation of human airway tone.

Sensory nerves regulate central and local reflexes such as airway plasma leakage, and cough, and their function is enhanced during inflammation. Dopamine, via the dopamine receptor agonists inhibits sensory nerve-induced microvascular leakage in the rat (14). Quinagolide (D(2/3) agonist), ropinirole (D(2/3/4) agonist), SKF 38393 (D(1/5) agonist), AR-C68397AA (Viozan) (dual D(2)/B(2) agonist) and dopamine all inhibit hypertonic saline induced depolarization by approximately 50% (14). Thus, dopamine receptor agonists may be of therapeutic benefit in the treatment of symptoms such as cough and mucus secretion which are evident in respiratory diseases such as asthma and chronic obstructive pulmonary disease.

### Neurotrophic Factors

The neurotrophins nerve growth factor (NGF), brain-

derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) play pivotal roles in the development of the nervous system (101). They also exert multiple actions on neuronal and non-neuronal cells, and neurotrophin receptors are expressed on central and peripheral neurons, lymphocytes, monocytes, mast cells, and fibroblasts and regulate inflammatory processes (106). Elevated neurotrophin concentrations are observed under pathological conditions in sera of patients with inflammatory disorders (107). Asthma, lung cancer, and pulmonary fibrosis are all associated with changes in the production of neurotrophins (101).

Patients with asthma feature both airway inflammation and an abnormal airway reactivity to many unspecific stimuli, referred to as airway hyper-responsiveness, which is, at least partly, under neuronal control. Interestingly, these patients show increased levels of neurotrophins in the blood, as well as locally in the lung. Neurotrophin release from immune cells is triggered by allergen contact. The presence of neurotrophins and the neurotrophin receptors p75 (p75NTR), tyrosine kinase A (TrkA), TrkB and TrkC are present in several immune cells. There is strong evidence for an involvement of neurotrophins in modulation of immune cell function in mature cells circulating in the blood or resting in lymphatic organs and peripheral tissues (101).

After segmental allergen provocation neurotrophin concentrations increase in the bronchoalveolar lavage (BAL) fluid from patients with asthma (137). Since neurotrophic factors increase nerve excitability and neurotransmitter synthesis and are produced by immunocompetent cells, they are likely candidates as mediators for the pathogenesis of asthma by causing inflammation and hyper-responsiveness.

Neurogenic switching is proposed as a hypothesis for a mechanism by which a stimulus at one site can lead to inflammation at a distant site. Neurogenic inflammation occurs when substance P and other neuropeptides released from sensory neurons produce an inflammatory response. Immunogenic inflammation however results from the binding of antigen to antibody or leukocyte receptors. There is a crossover mechanism between these two forms of inflammation. Neurogenic switching is proposed to result when a sensory impulse from a site of activation is rerouted via the CNS to a distant location to produce neurogenic inflammation at the second location. Neurogenic switching is a possible explanation for systemic anaphylaxis, in which inoculation of the skin or gut with antigen produces systemic symptoms involving the respiratory and circulatory systems. Food-allergy-inducing asthma, urticaria, arthritis, and fibromyalgia are other possible examples of neurogenic switching. Neurogenic switching provides a mechanism to explain how allergens, infectious agents, irritants, and possibly emotional stress can exacerbate conditions such as migraine, asthma, and arthritis. Because neurogenic inflammation is known to be triggered by chemical exposures, it may play a role in the sick building and multiple chemical sensitivity syndromes. Thus, neurogenic switching would explain how the respiratory irritants lead to symptoms at other sites in these disorders (94).

**Nerve growth factor (NGF)**

Allergic bronchial asthma is characterized by chronic inflammation of the airways, development of airway hyper-reactivity, and recurrent reversible airway obstruction. NGF participates in the development of bronchial hyper-responsiveness bronchoconstriction, airway hyperreactivity and inflammation (33, 42, 58). NGF regulates the growth of lung tumor cells and cultured lung fibroblasts (40, 58). Thus, neurotrophins, particularly NGF, are candidate molecules for regulating disease processes in asthma, lung cancer, and pulmonary fibrosis.

Different cell types are capable of secreting NGF: inflammatory cells that infiltrate the bronchial mucosa, and structural cells such as epithelial cells, smooth muscle cells and pulmonary fibroblasts. Furthermore, increased NGF levels are detected in the bronchoalveolar lavage fluid from asthmatic patients.

Treatment of sensitized and aerosol challenged BALB/c mice with anti-NGF antibodies, inhibit allergen-induced early-phase reaction and suppress airway inflammation (111). Transgenic mice constitutively over-expressing NGF in the airways (Clara-cell secretory protein promoter [CCSP]-NGF-tg) show early-phase reaction and airway inflammation compared with wild-type mice. These effects are paralleled by increased serotonin levels in the airways, whereas immunoglobulin E levels remain unaffected. Furthermore, CCSP-NGF-tg mice develop an increased reactivity of sensory neurons in response to inhaled capsaicin, demonstrating a NGF-mediated neuronal plasticity (111). These data support a functional role of NGF and suggest that NGF plays a role in the development of allergic early phase responses in the airways for inflammation, bronchial hyper-responsiveness and airway remodeling in asthma.

**Brain-derived neurotrophic factor (BDNF)**

BDNF production is enhanced during allergic airway inflammation by infiltrating T-cells, macrophages, and resident airway epithelial cells (16). Although BDNF itself does not influence airway inflammation, it is involved in inducing functional neuronal changes in allergic bronchial asthma, including the development

of allergen-induced neuronal hyper-reactivity in mice (16).

In patients, the chronic inflammation of asthma and reduced airway hyper-responsiveness can be brought about by low doses of a combination of an inhaled long-acting beta2-agonist (LABA) and a corticosteroid (ICS) (salmeterol / fluticasone and formoterol / budesonide) (10). LABA inhibits mast cell mediator release, plasma exudation, and may reduce sensory nerve activation (10). Corticosteroids increase the expression of beta2-receptors by increasing gene transcription, which protects against the loss of beta2-receptors in response to long-term exposure to beta2-agonists (10). While this is unlikely to be important in bronchodilator responses to beta2-agonists, it is probably important in preventing loss of beta-agonist effects on the non-bronchodilator actions of LABA.

Beta2-agonists may potentiate the molecular mechanism of corticosteroid actions, with increased nuclear localization of glucocorticoid receptors, and additive or synergistic suppression of inflammatory mediator release. Thus, LABA and ICS may optimize each others beneficial actions in the airways and the low systemic presence of these drugs do not lead to any increase in adverse effects.

**Adenosine**

Adenosine, a mediator of cerebral blood flow regulation, and neopterin, a macrophage-producing compound, are found in patients with ALS (144). Compared to control subjects, the adenosine levels are significantly elevated in the patients with acute-stage cerebral infarction, acute meningitis, and ALS. The neopterin levels are also significantly increased in patients with human T-lymphotropic virus type I-associated myelopathy/tropical spastic paraparesis, acute meningitis, and acute-stage cerebral infarction. The neopterin levels are directly correlated with the cell number and glucose levels in the cerebrospinal fluid (CSF), and are a sensitive marker of inflammation (144). The increased neopterin levels suggest that the mononuclear cellular infiltration remains for a long time.

**Cytokines**

A cell-derived hormone-like polypeptide that regulates cell replication, differentiation, or activation in processes related to host protection and repair. Within the CNS, cytokines stimulate inflammatory processes that can impair the permeability of the blood-brain barrier, as well as promote apoptosis of neurons, oligodendrocytes and induce myelin damage (60). Estrogen modulates cytokine expression making it an important link between hormonal-cytokine and neurodegeneration (29).

**Interleukin-6 (IL-6)**

IL-6 is present in the CSF of patients with ALS, but not control patients (124). The elevated IL-6 may reflect an humoral immune response, or IL-6 may be non-specifically expressed in these patients as a putative neurotrophic factor in response to nerve cell degeneration.

Mice, transgenic for the inflammatory cytokine interleukin-6 (IL-6), express high circulating levels of IL-6 from birth and show a marked decrease in growth rate leading to adult mice 50-70% the size of wild-type littermates (31). The growth defect is completely abolished by neutralizing IL-6. In these mice the production of GH is normal, while the circulating level of IGF-I is markedly decreased. Administration of IL-6 to wild-type mice results in a marked decrease in IGF-I levels. These observations show that in vivo high levels of IL-6 are associated with low levels of IGF-I. However, IL-6 does not directly affect IGF-I production both in vitro and in vivo. In contrast, markedly decreased levels of IGFBP-3 are present in the IL-6 transgenic mice and administration of IL-6 to wild-type mice results in a marked decrease in IGFBP-3 levels. In these mice the decrease in IGFBP-3 levels is associated with impaired formation of the 150 kD ternary complex, even in the presence of normally functional ALS. As a consequence, IL-6 transgenic mice show increased clearance of circulating IGF-I, suggesting that IL-6 decreases IGF-I levels by increased clearance. Proteolytic degradation of IGFBP-3 occurs in the IL-6 transgenic mice, suggesting that the decrease in IGFBP-3 could be at least in part due to proteolysis (32). The abnormalities of the IGF-I system observed in the IL-6 transgenic mice are similar to those found in patients with systemic juvenile idiopathic arthritis, one of the chronic inflammatory diseases characterized by stunted growth and prominent production of IL-6. The IL-6 transgenic mice represent a faithful animal model of the growth impairment associated with chronic inflammation and may therefore provide information relevant to the understanding and treatment of this complication of inflammatory diseases (31).

**Gene Expression**

High-density oligonucleotide microarray technology has allowed the determination of transcriptional profiles in postmortem spinal cord gray matter from individuals with ALS. The motor neuron-specific gene expression profile in sporadic ALS should help provide information on which genes lead to neurodegeneration and neuronal death. Such information should be extremely useful for developing new therapeutic strategies.

cDNA microarray technology has allowed the analysis of genes up-regulated following spinal cord trauma in G93A mice (61). The up-regulated genes were related to the

inflammatory process, such as tumor necrosis factor-alpha (TNF-alpha), resulting from glial cell activation, and apoptosis-related gene expression, such as caspase-1 (145). Other up-regulated genes are promoters for cell death pathway, death receptor 5, cyclins A1 and C, and caspases-1, -3, and -9, and cell death inhibitors, acetyl-CoA transporter, and NF-kappaB (61). Finally, genes for neuroprotective neurotrophic factors such as ciliary neurotrophic factor (CNTF), hepatocyte growth factor (HGF), and glial cell line-derived neurotrophic factor are also up-regulated (131).

Down-regulated genes included those associated with cytoskeleton/axonal transport, transcription, and cell surface antigens/receptors, such as dynactin, microtubule-associated proteins, and early growth response 3 (EGR3) (61). Inflammation-related genes, such as those belonging to the cytokine family, were not significantly up-regulated in either motor neurons or ventral horns (61). Thus, ALS parallels other neurodegenerative disorders, such as Alzheimer's and prion diseases, in which the inflammatory process are believed to participate directly in neuronal death.

Similar results were obtained from postmortem spinal cord gray matter from individuals with ALS and persons who had suffered spinal cord trauma (30). Moreover, alterations were found in genes involved in mitochondrial function, oxidative stress, excitotoxicity, apoptosis, cytoskeletal architecture, RNA transcription and translation, proteasomal function, and growth and signaling (30).

### Autoimmune Process

The majority of the many diffusely scattered lymphocytes in the anterior and lateral corticospinal tracts and anterior horns belong to the suppressor/cytotoxicity T-cell subset and are mixed with variable numbers of macrophages (132). Helper-inducer T-cells are rare and B-cells are conspicuously absent. Compared to controls, ALS specimens exhibit an increase in major histocompatibility complex (MHC) products and human leucocyte antigens (HLA) in the corticospinal tracts and anterior horns. The HLA-ABC antigens are expressed in the glial matrix of the spinal cord, and HLA-DR antigens are strongly expressed by large dendritic cells. In addition, macrophages and endothelial cells are labeled by HLA-DR. These findings suggest that an autoimmune process or infectious agent plays a role in ALS.

### Vascular endothelial growth factor gene (VEGF)

Mutations in the vascular endothelial growth factor gene (VEGF) appear to be involved in development of ALS (91). Riluzole, an inhibitor of glutamate release, and the only agent presently approved for clinical use, extends survival of the mouse model of ALS by a few months. A number of trophic factors, anti-inflammatory agents, and inhibitors of oxidative stress prolong survival in mouse models and are being tested in clinical trials. Gene transfer of VEGF or glial cell-line derived neurotrophic factor, anti-inflammatory COX-2 inhibitors, and minocycline have had particularly promising results in mice (91).

### Muscle fiber-derived insulin-like growth factor (Igf-1)

Mutations in the copper/zinc superoxide dismutase (mSOD1) gene are associated with a familial form of ALS, and their expression in transgenic mice produces an ALS-like syndrome. Skeletal muscles are the primary target for the dominant action of the inherited SOD1 mutation. Muscle-restricted expression of a localized insulin-like growth factor-1 (Igf-1) isoform maintains muscle integrity and enhanced satellite cell activity in SOD1(G93A) transgenic mice, inducing calcineurin-mediated regenerative pathways (36). Muscle-specific expression of the local Igf-1 (mIgf-1) isoform also stabilizes neuromuscular junctions, reduces inflammation in the spinal cord, and enhances motor neuronal survival in SOD1(G93A) mice, as well as delaying the onset and progression of the disease. Thus, muscle fibers appear to provide the appropriate factors, such as mIgf-1, that are required for neuron survival.

### Tumor necrosis factor (TNF)

Tumor necrosis factor (TNF) is implicated in the pathogenesis of ALS and elevated TNF levels are observed in animal models of motor neuron disease, and activation of the TNF system is observed in ALS patients. TNF-deficient mice are protected from experimental allergic encephalomyelitis in an animal model of multiple sclerosis (MS), and anti-TNF antibodies worsen the disease in MS patients suggesting it acts as a neurotoxic cytokine (45). However, other reports suggest that TNF serves neuroprotective and neurotrophic actions.

Multiprobe ribonuclease protection assays (RPAs) provide data on the expression of different cytokines and apoptosis-related genes, which may be associated with ALS. Apoptosis-related genes are generally unaffected, but multiple caspases death receptor components, and TNF are up-regulated (55). The cytokine expression changes precede bulk protein oxidation and apoptosis gene expression, and TNFalpha and its receptors may link inflammation to apoptosis in ALS (55).

### Capsases

Caspase-11 is a key regulator of caspase-1 and caspase-3 activation under pathological conditions. The expression

of caspase-11 is up-regulated in the spinal cord of superoxide dismutase 1 (SOD1) G93A transgenic mice, a mouse model of ALS, before the onset of motor dysfunction and remains at the high levels throughout the course of disease (65). The caspase-1- and caspase-3-like activities, as well as the level of interleukin-1beta, are significantly reduced in the spinal cord of symptomatic caspase-11-/-;SOD1 G93A mice compared with that of caspase-11+/-; SOD1 G93A mice. However, neurodegeneration, inflammatory responses, and the disease onset and progression in SOD1 G93A transgenic mice are not altered by the ablation of caspase-11 gene (65). Thus, although caspases may contribute to certain aspects of pathology in this mouse model of ALS, their inhibition is not sufficient to prevent neurodegeneration. Thus, inhibition of caspases may not be the best approach for a therapeutic method for the treatment of chronic neurodegenerative diseases.

## Glial Cells

Autopsy studies and animal experiments suggest that microglial cell inflammation is involved in inducting the pathogenesis of motor neurons and their death in ALS. Monocyte-chemoattractant protein (MCP-1) may play an important role in microglial recruitment. ALS patients have a significant higher level of MCP-1 in their CSF, but not serum, compared to the control subjects (142). Cerebrospinal fluid MCP-1 activity may be a sensitive marker for neuroinflammation in ALS, which would be useful for monitoring treatment trials in ALS (142).

Peroxisome proliferator-activated receptors (PPARs) are involved in the inflammatory process, and agonists of PPAR-alpha, -gamma, and -delta have anti-inflammatory effects both in vitro and in vivo. Pioglitazone, a peroxisome proliferator-activated receptor-gamma (PPAR-gamma) agonist, improves motor performance, delays weight loss, attenuates motor neuron loss, and extends survival (13%) of the ALS mice model, compared to untreated control littermates(71). Pioglitazone also reduces gliosis and iNOS, NFkappa-B, and 3-nitrotyrosine immunoreactivity in the spinal cords of G93A SOD1 transgenic mouse model of ALS (71).

The glial cells surrounding upper and lower motor neurons and degenerating descending tracts of ALS patients show a strong glial reaction (8). These reactive astrocytes contain protein inclusions, express inflammatory makers such as the inducible forms of nitric oxide synthase (iNOS) and COX-2, display nitrotyrosine immunoreactivity and down-regulate the glutamate transporter EAAT2.

Glial activation could be initiated by proinflammatory mediators secreted by motor neurons in response to injury, axotomy or muscular pathology. In turn, reactive astrocytes produce nitric oxide and peroxynitrite, which cause mitochondrial damage in cultured neurons and trigger apoptosis in motor neurons (8). Astrocytes may also contribute to the excitotoxic damage of motor neurons by decreasing glutamate transport or actively releasing the excitotoxic amino acid (8). In addition, reactive astrocytes secrete pro-apoptotic mediators, such as nerve growth factor (NGF) or Fas-ligand, a mechanism that may serve to eliminate vulnerable motor neurons (8).

## NO and Superoxide

Nitric oxide (NO), a universal signaling molecule, is involved in many physiological and pathophysiological processes, including asthmatic airway inflammation. Nitric oxide synthases (NOS) are enzyme systems active in airway epithelial cells, macrophages, neutrophils, mast cells, non-adrenergic non-cholinergic neurons, smooth muscle cells and endothelial cells. Two functional classes of NOS have been identified: the inducible form temporarily leading to large amounts of NO, and the constitutive form continuously leading to small amounts of NO. Large amounts of NO contribute to airway inflammation and killing of micro-organism, whereas small amounts of NO lead to smooth muscle relaxation. Asthmatic airway obstruction is induced by various bronchoconstricting factors (like allergens, pharmacological spasmogens, physical stimuli, infectious disease state) and is inhibited by NO (130). The development of specific inhibitors for the inducible form of NOS might open up a new era of antiasthmatic drugs.

Peroxynitrite is a product of the reaction between NO and superoxide (113, 114). Peroxynitrite is a strong oxidizing and nitrating agent which reacts with all classes of biomolecules. In the CNS it is generated by microglial cells, activated by pro-inflammatory cytokines or beta-amyloid peptide (beta-A), and by neurons in three different situations: hyperactivity of glutamate neurotransmission, mitochondrial dysfunction and depletion of L-arginine or tetrahydrobiopterin. The first two situations correspond to cellular responses to an initial neuronal injury in which the peroxynitrite exacerbates the inflammatory process, while in the third situation the generated peroxynitrite directly contributes to the initiation of the neurodegenerative process. Preventing the destructive effects of peroxynitrite requires blocking its synthesis, which involves preventing superoxide synthesis.

## Oxidative Stress

Asthma may be associated with oxidative stress which can be neurotoxic. Exercise by asthmatics can lead to oxidative stress which can be reduced by lycopene, a

natural antioxidant (103, 104).

Oxidative stress occurs when the production of damaging free radicals and other oxidative molecules exceeds the capacity of the body's antioxidant defenses to detoxify them. Oxidants also play an important positive role in the immune system. We live in an oxygen-rich environment and use oxygen to extract energy from food and as a corollary of this oxygen radicals are released. Thus, the production and control of reactive oxidants are integral life processes. However, these can be disrupted and oxidative stress can contribute to many diseases including inflammation, autoimmune diseases, cancer, neurodegenerative diseases, heart attack and stroke. It is necessary to understand the specific mechanisms of oxidative injury and whether antioxidant intervention is protective.

Free radicals are highly unstable molecules that interact quickly and aggressively with other molecules in our bodies to create abnormal cells. They are capable of penetrating into the cellular membranes, enzymes and DNA and damage or destroy them. Free radicals are unstable because they have unpaired electrons in their molecular structure, which causes them to react almost instantly with any substance in their vicinity. Oxygen, or oxyl, free radicals are especially dangerous. Free radicals are broken down into three broad groups: ROS (reactive oxygen species), RNS (reactive nitrogen species), and R (other reactive radicals). Despite their sometimes useful functions in the body, they are extremely unstable molecules that can damage cells if left uncontrolled. They accelerate aging and contribute to the development of many diseases, including cancer and heart disease.

The main antioxidants are vitamins A, E and C, betacarotene, glutathione, bioflavonoids, selenium, zinc, CoQ10 (ubiquinone), and various phyto-chemicals from herbs and foods. Green tea, for example, is rich in polyphenols—powerful anticarcinogens.

Biochemical antioxidants not only scavenge free radicals, but also inhibit their generation. They include lipoic acid, enzymes such as catalase, superoxide dismutase (SOD), glutathione peroxidase, and other repair enzymes. Melatonin, a hormone produced by the pineal gland, is also a potent antioxidant. Cholesterol, produced by the liver, is another major antioxidant that the body uses to repair damaged blood vessels. It is probably for this reason that serum cholesterol levels elevate as people age: with age comes more free radical activity. In response, the body produces more cholesterol to help contain and control the damage.

Of all the antioxidants, glutathione appears to be pivotal. Made up of three amino acids (cysteine, glycine, and glutamic acid), glutathione is part of the antioxidant enzyme glutathione peroxidase and is the major liver antioxidant. It is a basic tenet of natural medicine that health cannot exist if the liver is toxic. Not surprisingly, extremely low levels of glutathione are found in people suffering from severe OS. People with AIDS, cancer, and Parkinson's disease, for example, are known for their low glutathione levels.

Inflammatory lung diseases such as asthma and chronic obstructive pulmonary disease (COPD) are characterized by systemic and local chronic inflammation and oxidative stress (115). The sources of the increased oxidative stress in patients with asthma and COPD arise from the increased burden of inhaled oxidants, and from the increased amounts of reactive oxygen species (ROS) generated by several inflammatory, immune and structural cells of the airways (115). Increased levels of ROS produced in the airways are reflected by increased markers of oxidative stress in the airspaces, sputum, breath, lungs and blood in patients with asthma and COPD.

ROS, either directly or via the formation of lipid peroxidation products such as acrolein, 4-hydroxy-2-nonenal and F(2)-isoprostanes, appear to play a role in enhancing the inflammation through the activation of stress kinases (JNK, MAPK, p38, phosphoinositide 3 (PI-3)-kinase/PI-3K-activated serine-threonine kinase Akt) and redox sensitive transcription factors such as NF-kappaB and AP-1 (115). Oxidative stress and pro-inflammatory mediators can also alter nuclear histone acetylation/deacetylation allowing access for transcription factor DNA binding leading to enhanced pro-inflammatory gene expression in various lung cells (115). Furthermore, oxidative stress may alter the balance between gene expression of pro-inflammatory mediators and antioxidant enzymes in favor of inflammatory mediators in the lung (116). Thus, the presence of oxidative stress may have important consequences for the pathogenesis of asthma and COPD. In addition, the oxidative stress and chronic inflammation associated with the lungs, may also affect the CNS leading to oxidative stress and neuron death.

Future work is directed to understand the molecular mechanisms of antioxidants on ROS-mediated cell signaling pathways and inhibition of inflammatory response that would provide information for the development of novel antioxidant therapeutic targets in asthma and COPD. Effective wide spectrum antioxidant therapy that has good bioavailability and potency is urgently needed to control the localized oxidative and inflammatory processes that occur in the pathogenesis of asthma and COPD. In addition, development of such novel antioxidant compounds would be therapeutically useful in monitoring the oxidative and inflammatory biomarkers in the progression/severity of asthma and COPD.

### Mitochondria: Oxidative Stress

Mitochondrial dysfunction, cell energy impairment, apoptosis and overproduction of reactive oxygen species (ROS), is a final common pathogenic mechanism in aging and in neurodegenerative disease such as Alzheimer's disease (AD), Parkinson's disease (PD) and ALS. There are multiple apoptotic pathways stemming from mitochondria that play critical roles in apoptosis. The mitochondrial respiratory chain that produces cellular energy through oxidative phosphorylation by ATP synthesis is responsible for producing most ROS, including superoxide anion. In addition to activating the apoptosis program, ROS and reactive nitrogen species (RNS), although not directly responsible themselves for neuron death (38), are involved in the modulating critical cellular functions of neurons, astrocytes and microglia, such as, ion transport and calcium mobilization, which are involved in excitotoxicity. Nitric oxide, an RNS, is produced by three isoforms of NO-synthase in brain.

## Reducing the severity of ALS

### Cyclooxygenase 2 (COX-2)

During the development of ALS there is a dramatic increase in the expression of Cox-2, a key enzyme in the synthesis of prostanoids / prostaglandins (PGs), which are potent mediators of physiologic processes and inflammation (2). They are produced by two isoforms of the COX enzyme, COX-1 and COX-2. COX-2 is crucial for PG-synthesis in inflammation, while inhibition of COX-2 prevents the loss of motor neurons in an animal model of ALS. Furthermore, spinal COX-2 expression is increased in transgenic mice that produce an ALS-like syndrome (86).

COX-2 expression in the spinal cord of humans with sporadic ALS is dramatically higher than in control patients (86). The COX-2 genes are found in motor neurons, interneurons, and glial cells, whereas the COX-1 genes are predominantly confined to microglia (86). The concentration of prostaglandin E2 (PG E2), a marker for COX activity in the cerebrospinal fluid, is markedly increased in ALS cases compared to the non-ALS specimens. This supports the critical role of COX-2 in the pathogenesis of motor neuron death in ALS. This also suggests that Cox-2 inhibition may be a valuable tool for ALS treatment.

Oral administration of either celecoxib or rofecoxib, specific COX-2 inhibitors, significantly improve motor performance, attenuate weight loss and extended survival in the G93A transgenic mouse model of ALS. The administration of COX-2 inhibitors significantly delays in the onset of locomotor impairment in mice (2) and reduces prostaglandin E2 levels at 110 days of age (73). The combination of creatine with COX-2 inhibitors has additive neuroprotective effects and extends neuron survival by approximately 30% (73). The COX-2 inhibitors significantly protect against depletion of anterior horn motor neurons and creatine with COX-2 inhibitors showed greater protection than COX-2 inhibitors alone (73). Thus, combination therapies are an important strategy for the treatment of ALS.

### Anti-inflammatories

Eicosanoids are anti-inflammatory lipid mediators that play important roles in cell-cell communications, and as intracellular signals that are critical components of multi-cellular responses, such as acute inflammation and reperfusion injury. Lipoxins (LX) are trihydroxytetraene-containing eicosanoids generated within the vascular lumen during platelet-leukocyte interactions and at mucosal surfaces via leukocyte-epithelial cell interactions. During these cell-cell interactions, transcellular biosynthetic pathways are used as major LX biosynthetic routes, and thus, in humans, LX are formed in vivo during multi-cellular responses such as inflammation, atherosclerosis, and in asthma. This branch of the eicosanoid cascade generates specific tetraene-containing products that serve as stop signals, in that they regulate key steps in leukocyte trafficking and prevent leukocyte-mediated acute tissue injury (125). Aspirin's mechanism of action also involves the triggering of novel carbon 15 epimers of LX or 15-epi-LX that mimic the bioactions of native LX.

### Tetracyclines

Minocycline is a second-generation tetracycline with anti-inflammatory properties and it also inhibits microglial activation. Working with the mouse model, which expresses a mutant superoxide dismutase (SOD1(G37R)) linked to human ALS, minocycline delayed the onset of motor neuron degeneration, muscle strength decline, and increased the longevity of SOD1(G37R) mice by approximately 5 weeks for 70% of tested mice (76, 134). Further, minocycline treated animals have fewer activated microglia at both the early symptomatic stage (46 weeks) and the second stage of disease in the spinal cord of SOD1(G37R). Thus, interference with immuno-inflammatory responses has a beneficial effect in the ALS mice model.

### Opioids

Traditional anti-inflammatory drugs provide limited therapeutic use because of their narrow spectrum and severe side effects after long-term use. Morphinans (opioids) are a class of compounds containing the basic morphine structure that provide neuroprotective effects

in multiple inflammatory disease models (146). Thus, morphinians may provide a therapeutic neuroprotection against neuro-inflammation diseases.

Opioids resemble a group of regulatory peptides in nerve fibers within airway-innervating, and they influence a multitude of airway functions by modifying neural synaptic transmission. Their localization to neurons projecting into airways suggests their possible role as regulators of neurogenic inflammation, bronchoconstriction and mucus secretion. They mainly act through modification of tachykinergic and cholinergic transmission and inhibit bronchoconstriction (52).

In addition to the presence of the classical opioids and their receptors in the lung, a group of peptides (nociceptin and endomorphins) are present in the airways (52). Endomorphin-1 acts via the classical OP(3) (mu) receptor, while nociceptin binds to a new receptor termed opioid receptor-like-receptor (ORL(1)) and inhibits tachykinergic constriction (52). Unfortunately no effective therapeutic strategies have been developed to take advantage of their modulatory effects on airway smooth muscle tone.

**Insulin-like growth factor I (ILF-1)**

In vivo and in vitro insulin-like growth factor I (ILF-1) promotes motor neuron survival and strongly enhances motor nerve regeneration (141). Nine months of subcutaneous administration of ILF-1 leads to an increased length of survival of the transgenic mouse ALS model (97, 100, 141). Similarly, IGF-I provided neuroprotection against programmed death of embryonic rat spinal cord motor neurons in an in vitro model of ALS (136).

IGF-I binds to the IGF-I receptor (IGF-IR) of motor neurons, which activates MAPK and the downstream effector of phosphatidylinositol 3-kinase (PI-3K) signaling, Akt. IGF-I:IGF-IR signaling involves phosphorylation of IRS-1 and Shc, but not IRS-2. Glutamate, which is elevated in the cerebrospinal fluid of ALS patients, induced DNA fragmentation and caspase-3 cleavage in the spinal cord motor neurons. These effects of glutamate are blocked by co-treatment with IGF-I (136).

Although subcutaneous injection of ILF-1 has minimal influence on the progression of symptoms of ALS in patients(141), when administered intrathecally, ILF-1 modestly slows the decline of some motor functions, such as limb movement, but not of forced vital capacity (97, 100, 141). The limited clinical effects of IGF-1 in ALS patients and may be due to its inactivation by binding to IGF binding proteins (IGFBPs), and or limited delivery of IGF-I to motor neurons (141). Larger clinical studies are required to determine the efficacy of ILF-1, or analogues of ILF-1, for the treatment of patients with ALS, as well as of optimal doses and timing of IGF-1 delivery.

Recently using the mouse model of ALS it has been shown that a combination of insulin-like growth factor-1 gene delivery and exercise significantly increased animal survival and motor function (67). This is likely the result of synergistic effects of exercise and insulin-like growth factor-1. Thus, a drug treatment combined with appropriate exercise may provide a promising therapy for amyotrophic lateral sclerosis.

**Protection of Asthmatics**

Asthmatics are severely challenged by airway inflammation. However, the triggers of that inflammation have broader implications for inducing inflammation throughout the body, including the brain and spinal cord. Such inflammation in the CNS could lead to activation of glia and their resulting toxic influences on motor neuron survival. It may be critical to monitor the systemic inflammation of asthmatics to protect them from effects

**New Directions**

Additional approaches to those mentioned above for reducing the severity of ALS and asthma are:

1. Preventing glutamate neurotoxicity by blocking glutamate uptake by neurons and glia (75)
2. Increasing neuroprotection with inhibitors of cyclic nucleotide phosphodiesterases (PDEs) which increases the expression of cAMP response element binding protein (CREB) mRNA (105). PDE enzymes also degrade cyclic adenosine monophosphate (cAMP), which leads to modifying the response of the immune system to external stimuli (13).
3. The use of antioxidants, such as BHT (butylated hydroxy-toluene) to increase neuroprotection (147).
4. Blocking the production and action of tumor necrosis factor (TNF) to prevent it from inducing inflammation (36, 45). It will alsoreduce glutamate toxicity by inhibiting glutamate uptake (147).
5. Neuroprotection by inhibiting nuclear factor (NF)-kappaB family of transcription factors (112).
6. Low-dose chemotherapy to inhibit gliosis may prove beneficial in eliminating or reducing the toxicity of activated microglia ALS (18).
7. Estrogen replacement therapy may provide neuroprotection against ALS by its potent immunosuppressive, and anti-inflammatory activity on microglia (19).
8. Vitamin E supplementation reduces the severity and may even prevent the onset of ALS (41).

**Possible correlations between ALS and asthma**

The authors of this review knew a Puerto Rican woman who lived her entire life in Puerto Rico and suffered life-

long challenges with asthma and died of ALS. Although there are many close parallels between the manifestations of asthma and ALS we could not find any direct connection between the development of the two diseases. However, the development of both diseases in an individual suggests that a correlation exists between the etiology of asthma and that of ALS. Further research may lead to discovering the triggers of asthma and ALS, and whether a correlation exists.

## Conclusions

Asthma and ALS are related by both manifesting extensive and toxic inflammation. ALS is a progressive and incurable neurodegenerative disease, while asthma is a debilitating disorder. A number of approaches retard the progression of ALS in animal ALS models and reduce the symptoms of asthma. However, these techniques must probably be used simultaneously to effectively counteract the multifactorial causes of inflammation and triggers of motor neuron death. The authors of this review could not draw a direct connection between the development of ALS and asthma. However, the development of both diseases in several individuals in a relatively small community, strongly suggest the existence of a correlation. They also suggest that further studies should examine potential influences of anti-asthma medications as triggers of ALS.

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