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(54) Title: NRF2 SCREENING ASSAYS AND RELATED METHODS AND COMPOSITIONS

(57) Abstract: Provided are certain methods of screening, identifying, and evaluating neuroprotective compounds useful for treatment of neurological diseases, such as, e.g., multiple sclerosis (MS). The compounds described upregulate the cellular cytoprotective pathway regulated by Nrf2. Also provided are certain methods of utilizing such compounds in therapy for neurological disease, particularly, for slowing or reducing demyelination, axonal loss, or neuronal and oligodendrocyte death.

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Nrf2 SCREENING ASSAYS
AND RELATED METHODS AND COMPOSITIONS

[0001] Provided are certain compounds for treating neurological diseases, including demyelinating neurological diseases, such as, e.g., multiple sclerosis.

[0002] Multiple sclerosis (MS) is an autoimmune disease with the autoimmune activity directed against central nervous system (CNS) antigens. The disease is characterized by inflammation in parts of the CNS, leading to the loss of the myelin sheathing around neuronal axons (demyelination), loss of axons, and the eventual death of neurons, oligodenrocytes and glial cells.

[0003] An estimated 2,500,000 people in the world suffer from MS. It is one of the most common diseases of the CNS in young adults. MS is a chronic, progressing, disabling disease, which generally strikes its victims some time after adolescence, with diagnosis generally made between 20 and 40 years of age, although onset may occur earlier. The disease is not directly hereditary, although genetic susceptibility plays a part in its development. Relapsing-remitting MS presents in the form of recurrent attacks of focal or multifocal neurologic dysfunction. Attacks may occur, remit, and recur, seemingly randomly over many years. Remission is often incomplete and as one attack follows another, a stepwise downward progression ensues with increasing permanent neurological deficit.

[0004] Although various immunotherapeutic drugs can provide relief in patients with MS, none is capable of reversing disease progression, and some can cause serious adverse effects. Most current therapies for MS are aimed at the reduction of inflammation and suppression or modulation of the immune system. As of 2006, the available treatments for MS reduce inflammation and the number of new episodes but not all have an effect on disease progression. A number of clinical trials have shown that the suppression of inflammation in chronic MS rarely significantly limits the accumulation of disability through sustained disease progression, suggesting that neuronal damage and inflammation are independent pathologies. Promoting CNS remyelination as a repair mechanism and otherwise preventing axonal loss and neuronal death are some of the important goals for the treatment of MS. For a comprehensive review of MS and its current therapies, see, e.g., McAlpine's Multiple Sclerosis, by Alastair Compston et al., 4th edition, Churchill Livingstone Elsevier, 2006.

[0005] "Phase 2 enzymes" serve as a protection mechanism in mammalian cells against oxygen/nitrogen species (ROS/RNS), electrophiles and xenobiotics. These enzymes are not normally expressed at their maximal levels and, their expression can be induced by a variety of natural and synthetic agents. Nuclear factor E2-related factor 2 (Nrf2) is a transcription factor responsible for the induction of a variety of important antioxidant and detoxification enzymes that coordinate a protective cellular response to metabolic and toxic stress.

[0006] *ROS/RNS are most damaging in the brain and neuronal tissue,* where they attack post-mitotic (i.e., non-dividing) cells such as glial cells, oligodendocytes, and neurons, which are particularly sensitive to free radicals. This process leads to neuronal damage. Oxidative stress has been implicated in the pathogenesis of a variety of neurodegenerative diseases, including ALS, Alzheimer's disease (AD), and Parkinson's disease (PD). For review, see, e.g., van Muiswinkel et al., Curr. Drug Targets CNS--Neurol. Disord., 2005, 4:267-281. An anti-oxidative enzyme under control of Nrf2, NQO1 (NAD(P)H dehydrogenase, quinone (1), was recently reported to be substantially upregulated in the brain tissues of AD and PD subjects (Muiswinkel et al., Neurobiol. Aging, 2004, 25: 1253). Similarly, increased expression of NQO1 was reported in the ALS subjects' spinal cord (Muiswinkel et al., Curr. Drug Targets--CNS. Neurol. Disord., 2005, 4:267-281) *and in active and chronic lesions in* the brains of patients suffering from MS (van Horssen et al., Free Radical Biol. & Med., 2006, 41 311-311). These observations indicate that the Nrf2 pathway may be activated in neurodegenerative and neuroinflammatory diseases as an endogenous protective mechanism. Indeed, most recently, it has been reported that induced activation of Nrf2-dependent genes by certain cyclopenanone-based compounds (NEPP) counters the toxic effects of metabolic inhibition and ROS/RNS production in the brain and protects neurons from death in vitro and in vivo (see Satoh et al., PNAS, 2006, 103(3):768-773).

[0007] Additionally, many publications have reported neuroprotective effects of compounds in natural plant-derived compounds ("phytochemicals"), including α-tocopherol (vitamin E), lycopene (tomatoes), resveratrol (red grapes), sulforaphane (broccoli), EGCG (green tea), etc. For review, see Mattson and Cheng, Trends in Neurosci., 2006, 29(11):632-639. Originally, the action of these compounds was attributed to their anti-oxidant properties. However, while most anti-oxidants are effective only at high concentrations, at least some of these compounds appear to exert neuroprotective effects at much lower doses. Emerging evidence suggests that these compounds may exert their neuroprotective effects by activating cellular stress-response pathways, including the Nrf2 pathway, resulting in the upregulation of neuroprotective genes. However, the exact mechanism of action of these compounds remains poorly understood.

[0008] To date, more than 10 different chemical classes of inducers of Nrf2 pathway have been identified including isothiocyanates and their thiol addition products, dithiocarbamates, as well as 1,2-dithiole-3-thiones, trivalent arsenic derivatives (e.g., phenyl arsenoxide), heavy metals, certain conjugated cyclic and acyclic polyenes (including porphyrins, chlorophyllins, and chlorophyll), and vicinal dimercaptans. These inducers have few structural similarities. They are mostly electrophiles, and all can react chemically with thiol groups by alkylation, oxidation, or reduction, suggesting that the intracellular sensor for inducers is likely to contain very highly reactive (cysteine) thiols. The inducers can modify thiol groups by a variety of mechanisms including: alkylation (Michael addition acceptors, isothiocyanates, quinones); oxidation (e.g., peroxides and hydroperoxides); and direct reaction with thiol/disulfide linkages (e.g., vicinal dithiols such as 1,2-dimercaptopropanol, lipoic acid). These diverse response mechanisms provide plasticity for cellular responses to a variety of electrophilic and oxidant stressors.

[0009] Provided are methods that comprise at least one of the following methods:

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