

METHODS AND COMPOSITIONS FOR TREATING STATUS EPILEPTICUS AND SEIZURES CAUSING STATUS EPILEPTICUS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. APPLICATION Ser. No. 61/104,388, filed 10 Oct. 2008, and U.S. Application Ser. No. 61/104,311, filed 10 Oct. 2008, both of which are herein incorporated by reference in their entirety.

ACKNOWLEDGEMENT OF GOVERNMENT SUPPORT

[0002] This invention was made by employees of the United States Army Medical Research and Materiel Command. The Government has rights in this invention.

BACKGROUND OF THE INVENTION

[0003] 1. Field of the Invention

[0004] The present invention generally relates methods and compositions for treating seizures, seizures which cause status epilepticus, status epilepticus, and neuropathogenesis caused by cholinesterase inhibitors. The present invention also generally relates methods and compositions for treating seizures, seizures which cause status epilepticus, status epilepticus, and neuropathogenesis caused by overstimulation of the NMDA receptor pathway.

[0005] 2. Description of the Related Art

[0006] Organophosphate (OP) compounds inhibit the catalytic sites of cholinesterases (ChE), such as acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Inhibition of AChE leads to a build up of acetylcholine (ACh) in the central nervous system (CNS) and peripheral nervous system (PNS) that disrupts cholinergic neurotransmission. Exposure to OP compounds can induce seizures. If the seizures persist, neuropathogenesis (which leads to neuropathology, e.g. neuronal damage) and status epilepticus (SE) may result. SE is characterized by prolonged epileptic seizures that can produce long-term CNS damage and behavioral alterations in survivors and can cause death if untreated. It should be noted that not all OP compounds result in seizures or SE. In addition, some OP compounds may result in SE at one amount, but not another. See e.g. Crawford et al. (2004) (published online at handle.dtic.mil/100.2/ADA449679).

[0007] The mechanisms of OP induced seizures are generally divided into three phases. See McDonough & Shih (1997) *Neurosci Biobehav Rev* 21:559-579; and Carpentier (2008) *J Med CBR Def* 6 (published online). The first phase involves cholinergic based mechanisms, i.e. changes in brain AChE and accumulation of ACh, which begins from the time of exposure to about 5 min after seizure onset. The second phase is a transitional phase which is a combination of cholinergic and non-cholinergic based mechanisms, wherein excitatory amino acids (EAA) and glutamate are released, which over-stimulate N-methyl-D-aspartate (NMDA) receptors. The third phase comprises predominantly non-cholinergic based mechanisms. If seizure activity is not stopped before increased concentrations of glutamate result in glutamate neurotoxicity progression to SE often occurs.

[0008] Currently, seizures are treated with benzodiazepines, phenytoin, fosphenytoin, barbituates, and/or anes-

thetics. However, many of these treatments are ineffective against seizures induced by OP compounds and nerve agents.

SUMMARY OF THE INVENTION

[0009] The present invention provides a method of treating, preventing, inhibiting, or reducing a seizure, such as a SE causing seizure, status epilepticus, neuropathogenesis, or a neuropathology caused by exposure to an organophosphate compound in a subject in need thereof which comprises administering to the subject Pro-2-PAM, a huperzine compound, or both. In some embodiments, the present invention is directed to a method of increasing the survivability of a subject exposed, such as by cutaneous exposure, to an organophosphate compound which comprises administering to the subject Pro-2-PAM, a huperzine compound, or both. In some embodiments, Pro-2-PAM and/or the huperzine compound is administered before, during or after exposure to the organophosphate compound. In some embodiments, Pro-2-PAM and the huperzine compound are administered at the same time, different times, or both. In some embodiments, the huperzine compound is administered as an enantiopure composition or as a mixture.

[0010] In some embodiments, administration of Pro-2-PAM and/or the huperzine compound suppresses, eliminates, or protects the subject against seizure activity, seizures, such as an SE causing seizure, status epilepticus, neuropathogenesis, or a neuropathology caused by exposure to an organophosphate compound. In some embodiments, administration of Pro-2-PAM and/or the huperzine compound restores brain AChE activity.

[0011] In some embodiments, the present invention is directed to treating, preventing, inhibiting, or reducing a seizure, such as a SE causing seizure, status epilepticus, neuropathogenesis, or a neuropathology caused by exposure to an organophosphate compound in a subject in need thereof which comprises reactivating the extracellular AChE in the brain of the subject by administering Pro-2-PAM to the subject.

[0012] In some embodiments, the present invention provides a kit which comprises Pro-2-PAM and the huperzine compound packaged together. In some embodiments, the kit further comprises at least one device, such as an autoinjector, for delivering Pro-2-PAM, the huperzine compound, or both to a subject. In some embodiments, the autoinjector comprises a first compartment containing Pro-2-PAM and a second compartment containing the huperzine compound.

[0013] In some embodiments, the present invention provides a composition comprising Pro-2-PAM and the huperzine compound.

[0014] In some embodiments, the present invention provides a method of treating, preventing, inhibiting, or reducing a seizure, such as a SE causing seizure, status epilepticus, neuropathogenesis, or a neuropathology caused by overstimulation of the NMDA receptor pathway in a subject in need thereof which comprises administering to the subject a huperzine compound. In some embodiments, the huperzine compound is administered before, during or after the NMDA receptor pathway is overstimulated. In some embodiments, the huperzine compound is administered as an enantiopure composition or as a mixture. In some embodiments, the overstimulation of the NMDA receptor pathway is caused by a brain injury such as a penetrating traumatic brain injury (e.g.