

The number of animals is in brackets. * indicates significant difference between Pro-2-PAM and 2-PAM treatments; $p \leq 0.05$.

[0035] FIG. 11 shows brain (frontal cortex) AChE activity (mU/mg) at 24 hr after treatment with Pro-2-PAM at indicated times after DFP exposure. These data show that Pro-2-PAM reactivated DFP-inhibited brain AChE when given up to 40 min post-OP exposure. Numbers above points are number of animals tested. Dashed lines are average AChE activity for Pro-2-PAM treated animals (black dashed) compared to DFP only animals (gray dashed). * indicates significant difference between Pro-2-PAM treatment and DFP without oxime treated animals; $p \leq 0.05$.

[0036] FIG. 12 provides the structural formulas of examples of huperzine A compounds which may be administered in place of or in conjunction with +HupA. Huperzine A compounds TSK-V-3 [-]-19, TSK-V-4 [+]-19, TSK-IV-90B [-]-18, TSK-IV-78B and [+]-dimethylhuperzine showed protective efficacy against NMDA and DFP toxicity in cell culture. Huperzine A compounds TSK-V-3 [-]-19, TSK-V-4 [+]-19, and TSK-IV-90B [-]-18, were found to be protective against neuropathology resulting from exposure to DFP and soman.

DETAILED DESCRIPTION OF THE INVENTION

[0037] The present invention is directed to methods and compositions for treating, preventing, inhibiting, or reducing seizures, status epilepticus causing seizures, status epilepticus (SE), neuropathogenesis, and neuropathologies caused by exposure to a cholinesterase inhibitor which comprise administering to a subject in need thereof a therapeutically effective amount of Pro-2-PAM, a Huperzine compound, or both. The present invention is also directed to methods and compositions for treating, preventing, inhibiting, or reducing seizures, SE causing seizures, SE, neuropathogenesis, and neuropathologies caused by overstimulation of the NMDA receptor pathway, which overstimulation may be caused by a brain injury, which comprise administering to a subject in need thereof a therapeutically effective amount of a Huperzine compound.

[0038] As used herein, a "cholinesterase inhibitor" refers to a compound which inhibits a cholinesterase (ChE), e.g. acetylcholinesterase (AChE), from breaking down its substrate, e.g. acetylcholine (ACh). Cholinesterase inhibitors include organophosphate (OP) compounds, diisopropyl-n-fluorophosphate, OP insecticides, such as azinphos-methyl (Guthion, Guthion), bornyl (Swat), dimefos (Hanane, Pestox XIV), methamidophos (Supracide, Ultracide), methyl parathion (E 601, Pennacp-M), chlorpyrifos, Dichloroves, paraoxon, and Demeton S, and OP nerve agents, such as cyclosarin, sarin, soman, tabun, VR, VX, Novichok-5 and Novichok-7, and the like.

[0039] As used herein, "status epilepticus" is defined as one continuous unremitting seizure lasting longer than 30 min, or recurrent seizures without regaining consciousness between seizures for greater than 30 min.

[0040] As used herein, an "SE causing seizure" are those which lead to SE if not treated, prevented, inhibited or reduced and is typically one that last for more than about 5 min to about 30 min.

[0041] As set forth herein, a "huperzine compound" refers to synthetic and natural huperzine compounds known in the art. See e.g. US Pat. Publ. 20080090808. "Huperzine A" (HupA) refers to 9-amino-13-ethylidene-11-methyl-4-azatri-

cyclo[7.3.1.0]trideca-3(8),6,11-trien-5-one. The (-) and (+) enantiomers of HupA are indicated as -HupA and +HupA, respectively. The designation "HupA" refers to -HupA, +HupA, or both. "±HupA" is used to indicate a racemic mixture of +HupA and -HupA. The phrase "huperzine A compound" refers to HupA and analogs, derivatives, salts, hydrates, homologs, positional isomers, and stereoisomers thereof. Examples of huperzine A compounds include those set forth in U.S. Pat. Nos. 4,929,731; 5,106,979; 5,663,344; and 5,869,672; 5,104,880; 5,177,082; 5,929,084; and 5,547,960; dihydro-desmethyl-huperzine; 11-desmethyl-11-chloro-huperzine A, those shown in FIG. 12, and the like. Preferred huperzine compounds do not result in cardiotoxicity.

[0042] As used herein, "Pro-2-PAM" refers to N-methyl-1,6-dihydropyridine-2-carbaldoxime and salts and solvates thereof. Pro-2-PAM may be synthesized using methods known in the art. See e.g. Bodor (1976) J. Med. Chem. 19:102-107. Pro-2-PAM can be stored as a readily water soluble powder, similar to the oxime HI-6, and administered using methods and devices known in the art.

[0043] As used herein, a "subject" includes animal subjects and human subjects. A subject is considered to be "in need" of the treatments and compositions according to the present invention is considered to be a subject exposed to or at risk of exposure to an amount of a cholinesterase inhibitor which amount is likely to result in SE and/or neuropathogenesis if untreated.

[0044] As used herein, "neuropathogenesis" refers to the process of neuronal degeneration, seizure, apoptosis, necrosis, aberrant cell signaling, energy depletion, calcium toxicity, excitatory amino acid toxicity, oxidative stress, and inflammation.

[0045] As used herein, a "neuropathology" refers to the result of CNS neuropathogenesis such as neuronal damage, neuronal degeneration, neuronal cell death, swollen brain tissue, abnormal brain structures, pyramidal neuron layer disruption, deformed neuronal nuclei, axonal injury, neurobehavioral deficits, and the like.

[0046] The phrase "a therapeutically effective amount" refers to an amount of a given drug or compound, e.g. +HupA or Pro-2-PAM, which when administered to a subject is of sufficient quantity to achieve the intended purpose, such as to prevent, reduce or inhibit SE causing seizures, SE, neuropathogenesis, a neuropathology, or a combination thereof caused by overstimulation of the NMDA receptor pathway or exposure to an OP compound. Of course, the actual amount will depend upon a variety of factors including, inter alia, the timing of the administration, the condition being treated, the presence of other concurrent diseases or disorders, the age, weight, and general health of the subject. Determination of a therapeutically effective amount and timing of administration is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure herein and the dosages described herein are exemplary dosages which can be used as a guideline.

Huperzine A

[0047] Huperzine A (HupA) is an alkaloid and a ChE inhibitor which leads to an increase in ACh. -HupA has a much higher affinity for AChE than +HupA. See McKinney et al. (1991) Eur Pharmacol 203:303-305. In particular, +HupA