

those caused by bullets, shrapnel, etc.) or a blast induced traumatic brain injury (i.e. closed head injury, e.g. those caused by bombs).

**[0015]** In some embodiments, the present invention is directed to a medicament for treating, preventing, inhibiting, or reducing a seizure, such as a SE causing seizure, status epilepticus, neuropathogenesis, or a neuropathology which comprises Pro-2-PAM and/or a huperzine compound. In some embodiments, the seizure, the SE causing seizure, SE, neuropathogenesis, or the neuropathology is caused by overstimulation of the NMDA receptor pathway or exposure to an OP compound. In some embodiments the overstimulation of the NMDA receptor pathway is caused by a brain injury.

**[0016]** In the above embodiments and other embodiments as disclosed herein, the huperzine compound may be a huperzine A compound, preferably +HupA. In the above embodiments and other embodiments as disclosed herein, Pro-2-PAM, the huperzine compound, or both may be provided as a single dose or multiple doses. In the above embodiments and other embodiments as disclosed herein, Pro-2-PAM and the huperzine compound are provided in therapeutically effective amounts. In some embodiments, the therapeutically effective amounts are amounts which treat, prevent, inhibit, or reduce a seizure, an SE causing seizure, status epilepticus, neuropathogenesis, or a neuropathology caused by exposure to an organophosphate compound as compared to a control. In some embodiments where the seizure, the SE causing seizure, status epilepticus, neuropathogenesis, or the neuropathology is caused by overstimulation of the NMDA receptor pathway not involving exposure to an OP compound, such as a brain injury, therapeutically effective amounts of the huperzine compound are ones which treat, prevent, inhibit, or reduce a seizure, an SE causing seizure, status epilepticus, neuropathogenesis, or a neuropathology as compared to a control. In the above embodiments and other embodiments as disclosed herein, 2-PAM, a second huperzine compound, a supplementary active compound, or a combination thereof may be administered.

**[0017]** Both the foregoing general description and the following detailed description are exemplary and explanatory only and are intended to provide further explanation of the invention as claimed. The accompanying drawings are included to provide a further understanding of the invention and are incorporated in and constitute part of this specification, illustrate several embodiments of the invention, and together with the description serve to explain the principles of the invention.

#### DESCRIPTION OF THE DRAWINGS

**[0018]** This invention is further understood by reference to the drawings wherein:

**[0019]** FIG. 1A, Panel A shows EEG data that is representative of a saline control rat administered only PB and saline. Panel B shows EEG data for a DFP control animal. Each line represents one hour of EEG recording and 12 hr of recordings are shown. The scale on the Y-axis is  $-1$  mV to  $+1$  mV. Time and dose of drugs administered are indicated with arrows.

**[0020]** FIG. 1B shows a 10 sec segment of EEG data from one saline control animal. It is taken from 3 hr after saline administration. Y-axis scale is  $-1$  mV to  $+1$  mV.

**[0021]** FIG. 1C shows a 10 sec segment of EEG data from one DFP exposed control animal. It is taken from 3 hr after DFP administration. Y-axis scale is  $-1$  mV to  $+1$  mV.

**[0022]** FIG. 2A shows EEG data that is representative of a rat pre-treated with +HupA and then exposed to DFP. Each line represents 1 hr of EEG recording and 12 hr of recordings are shown. The scale on the Y-axis is  $-1$  mV to  $+1$  mV. Time and dose of drugs administered are indicated with arrows.

**[0023]** FIG. 2B is a 10 sec segment of EEG data from one animal pre-treated with +HupA is shown here. It is taken from 3 hr after DFP administration. Y-axis scale is  $-1$  mV to  $+1$  mV.

**[0024]** FIG. 3A shows EEG data for a rat treated with +HupA 1 min after DFP exposure. Each line represents 1 hr of EEG recording and 12 hr of recordings are shown. The scale on the Y-axis is  $-1$  mV to  $+1$  mV. Time and dose of drugs administered are indicated with arrows.

**[0025]** FIG. 3B is a 10 sec segment of EEG data from one rat treated with +HupA 1 min after DFP exposure. It is taken from 3 hr after DFP administration. Y-axis scale is  $-1$  mV to  $+1$  mV.

**[0026]** FIG. 4A shows EEG data for a rat treated with +HupA 5 min after DFP exposure. Each line represents 1 hr of EEG recording and 12 hr of recordings are shown. The scale on the Y-axis is  $-1$  mV to  $+1$  mV. Time and dose of drugs administered are indicated with arrows.

**[0027]** FIG. 4B is a 10 sec segment of EEG data from one rat treated with +HupA 5 min after DFP exposure. It is taken from 3 hr after DFP administration. Y-axis scale is  $-1$  mV to  $+1$  mV.

**[0028]** FIG. 5A shows EEG data for one rat treated with +HupA 10 min after DFP exposure. Each line represents 1 hr of EEG recording and 12 hr of recordings are shown. The scale on the Y-axis is  $-1$  mV to  $+1$  mV. Time and dose of drugs administered are indicated with arrows.

**[0029]** FIG. 5B is a 10 sec segment of EEG data from one rat treated with +HupA 10 min after DFP exposure. It is taken from 3 hr after DFP administration. Y-axis scale is  $-1$  mV to  $+1$  mV.

**[0030]** FIG. 6 shows representative EEG traces for Control, DFP, DFP then 2-PAM, and DFP then Pro-2-PAM treated guinea pigs. Animals received the standard military paradigm, e.g. 2-PAM 1 min post-exposure except for Pro-2-PAM treatment which was delayed by 15 min. Each line of EEG data represents 2 hr of recording. Thus, a full 24 hr are shown (12 lines) for each animal treatment. Solid circle indicates time of DFP exposure.

**[0031]** FIG. 7 shows H&E stains of guinea pig brain samples at  $40\times$  magnification of the piriform cortical neuron layer. Panel (a) is Control brain; Panel (b) is brain from animal receiving DFP only; Panel (c) is brain from animal receiving DFP followed by Pro-2-PAM; and Panel (d) is brain from animal receiving DFP followed by 2-PAM. Arrows point to piriform neurons.

**[0032]** FIG. 8 shows fluoro-jade stains of guinea pig brain samples at  $40\times$  magnification, of the hippocampus pyramidal neuron layer. Panel (a) is Control brain; Panel (b) is brain from animal receiving DFP followed by 2-PAM; and Panel (c) is brain from animal receiving DFP then Pro-2-PAM. Arrows point to hippocampus pyramidal neurons.

**[0033]** FIG. 9 shows blood AChE activity (U/ml) at 1.5 hr post treatment. These data show 2-PAM and pro-2-PAM equivalence for peripheral reactivation of DFP-inhibited AChE. Numbers in brackets are animals tested.

**[0034]** FIG. 10 shows AChE activity (mU/mg) in eight specific brain regions from guinea pigs 1.5 hr after treatment with saline (Control, ●), PB (▼), DFP only (□), or animals treated with DFP followed by 2-PAM (■) or pro-2-PAM (▲).