Establishing a relationship between nerve agent-induced seizures and body temperature

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Introduction

Chemical warfare is a threat that has no bias to soldiers or civilians. Nerve agent (NA) in chemical warfare causes over-excitation of the brain by inhibiting degradation of the neurotransmitter acetylcholine (ACh). The resulting build up of ACh can lead to status epilepticus (SE), a neurological state of emergency that can cause permanent brain damage and death if not treated immediately (McDonough et al., 1998). Unfortunately, current treatments for NA-induced SE are ineffective if administered too long after SE onset, which renders many vulnerable to unexpected exposures. Thus, there is a need for alternative interventions that can still treat NA poisoning after drug resistance has developed within the body.

A potential intervention is medically-induced hypothermia. This intervention utilizes the relationship between body temperature and seizures to stop a seizure event. It is known that high temperatures can cause febrile seizures. Inversely, medically-induced hypothermia has proved to terminate SE and prevent development of brain damage that causes epilepsy (Liu et al., 1993). This study hypothesizes that there may be specific periods during NA-induced seizures where temperature fluctuates. These periods would indicate windows of opportunity to use an intervention like hypothermia to improve outcomes for NA casualties.

Materials and Methods

Nine mice were exposed to soman and experienced prolonged SE followed by a series of spontaneous recurrent seizures (SRS), representing epilepsy in a mouse. Telemetry devices were implanted under the skin to monitor body temperature (°C) and brain waves via electroencephalogram (EEG) for six weeks post-exposure. It is worth mentioning that one of the mice were omitted from the total sample set due to faulty telemetry readings. NeuroScore (Figure 1a and b) was used to identify epileptiform activity and extract temperature readings at time points of interest within epileptiform activity (Abdullah & Islam, 2012). The data was then exported to Excel to generate various data tables and graphs. Pearson correlation tests, mixed-effect model analysis, and Tukey's multiple comparison tests were performed in Prism and Minitab. The results were then utilized to draw conclusions regarding viability of future research regarding NA-induced seizures and body temperature.

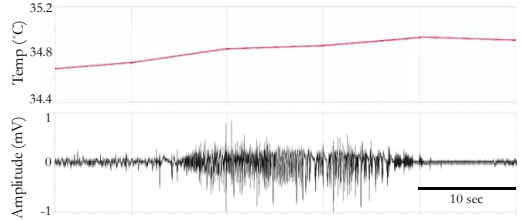


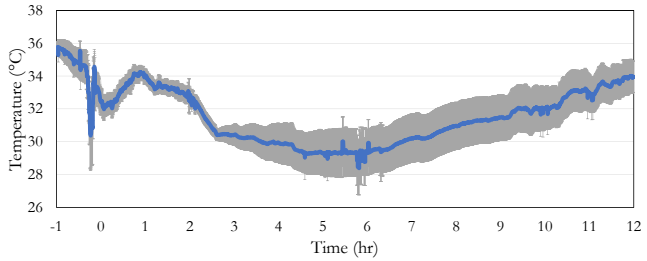
Figure 1a (left): An example of temperature in NeuroScore.

Figure 1b (left): An example of EEG in NeuroScore.

Results

For all mice in the study, average temperature over time was plotted for 1 hour before and 12 hours after nerve agent exposure (Graph 1). For the first 2.5 hours after nerve agent exposure, there was a consistent pattern of an initial increase in temperature followed by a steady decline. Recovery was much more variable between mice, with some reaching lower temperatures and taking longer to return to baseline.

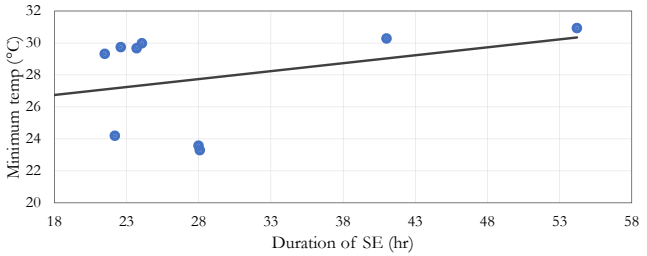
Average temperature over time



Graph 1 (above): A scatterplot displaying the average trend of temperature over time immediately before nerve agent exposure and during nerve agent-induced SE.

Six Pearson correlations compared various variables within the experiment to find any underlying trends within the data. There was a positive correlation between minimum temperature and duration (Graph 2) of SE, $r = 0.34$, $n = 9$, $p = 0.365$; a positive correlation between minimum temperature and duration of SE, $r = 0.31$, $n = 9$, $p = 0.412$; a negative correlation between minimum temperature and duration of SE, $r = -0.41$, $n = 9$, $p = 0.275$; a negative correlation between minimum temperature and duration of SE, $r = -0.16$, $n = 9$, $p = 0.677$; a negative correlation between minimum temperature and duration of SE, $r = -0.31$, $n = 9$, $p = 0.42$; a negative correlation between minimum temperature and duration of SE, $r = -0.28$, $n = 9$, $p = 0.462$. All correlation tests resulted in no significant association between their respective variables.

Duration of SE vs. minimum temperature

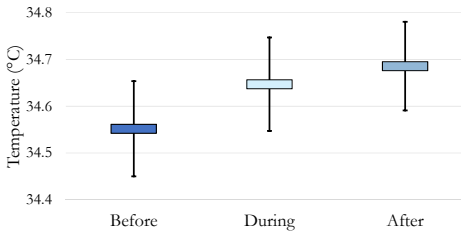


Graph 2 (above): A correlation graph displaying that there is no relationship between duration of status epilepticus and minimum temperature achieved within the initial status event.

Results (cont.)

A mixed-effect model compared body temperature during the three specified periods of an SRS and determined there was a significant effect of time on temperature, $F(1.603,848.0) = 22.20$, $p < 0.0001$ (Graph 3). A Tukey multiple comparisons test identified a significant difference between before vs. during, and before vs. after with a common $p < 0.0001$. No significant difference was discovered between during vs. after, $p = 0.2323$.

Average temperature relative to SRS



Graph 3 (left): The mixed-effect model compared the average body temperature 30 seconds prior, during, and 30 seconds after an SRS. A mixed-effect model was used to account for the missing values within the data that were created due to noise or interference.

Conclusion

The purpose of this study was to understand the relationship between nerve agent-induced seizures and body temperature. Examination of body temperature during nerve agent-induced SE revealed minimal variation between mice at the beginning of SE followed by larger variation during recovery, suggesting that interventions during the first 2 hours of SE would have the most predictable effects. Additionally, causing hypothermia during the later hours of SE probably wouldn't help based on the absence of significant correlations between lower minimum body temperatures during SE and improved outcomes like shorter SE duration, faster return to baseline temperature, and fewer subsequent SRS. During the SRS that developed over the next several weeks, mice in this study had a significant increase in body temperature during and after seizures, which may provide another window of opportunity for helpful interventions. Future research will examine whether chronic, low-grade hypothermia during the weeks following nerve agent exposure can reduce the development of SRS or prevent progression of brain damage.

References

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