A model of fever-induced seizures in African Naked Mole-Rats

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Introduction

Fever-induced (“febrile”) seizures are the most common neurological reason for emergency room visits in children, affecting 2-5% of children before the age of six (Verity et al. 1985). While the majority of brief febrile seizures are benign, they do increase the risk of subsequent febrile seizures, psychiatric disorders, and full-blown epilepsy (Dreier et al., 2019). Animal models of febrile seizures are useful to elucidate the mechanisms that drive these seizures and the changes in the brain they produce. Current animal models of febrile seizures use approaches to heat rats or mice, either the whole body or the head, during the first three weeks after birth (Dubé, et al., 2005; Schuchmann et al., 2006). After the third week of life, rats and mice undergo developmental shifts which make them resistant to hyperthermia-induced seizures. Therefore, models of febrile seizures in these species are limited to a short period of rapid development.

African naked mole-rats (NM-R, Figure 1) are rodents which demonstrate a delayed development and retain neonatal characteristics over their long lifespan (Skulachev, et al., 2017). NM-R also have a diminished ability to control their body temperature (Buffenstein & Yahav, 1991). We have recently demonstrated that NM-R exhibit hyperthermia-induced seizures well into adulthood, likely due to a genetic mutation driving decreased GABA function (Zions et al., 2020). When NM-R are placed in a warm environment, they reliably demonstrate epileptic seizures (Figure 2).

Polyinosinic: polyribidylic acid (poly[i.c.]) is a synthetic double stranded RNA molecule which acts as a viral mimic and produces an immune response (including fever) in other laboratory mammals (Nealis et al., 1978; Maxen, 1980). We proposed that NM-R would experience a rise in temperature following an injection of poly[i.c.]. Consequently, we hypothesized that the fever response would trigger a febrile seizure based upon previous warm-air induced seizures in NM-R. If successful, this approach would generate a true febrile seizure animal model, which will allow us to better understand the causes and consequences of febrile seizures in children.

Methods

Adult naked-mole rats were removed from their colony and placed in a beaker in a chamber with a ceramic heat emitter set to maintain the animal at a temperature between 31 and 35 °C. The animals were left in the chamber for 40 minutes to acclimate. After the acclimation period, NM-R were injected subcutaneously with either 5 or 10mg/kg poly[i.c.]. The animals remained in the chamber while their cutaneous temperature was measured approximately every five minutes using an infrared temperature gun. Behavior was monitored and recorded.

Figure 1. African naked mole-rat huddle

Figure 2. Cortical EEG recording of adult NM-R demonstrating a hyperthermia-induced seizure in a heated chamber. Adapted from Zions et al. 2020.

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References


Figure 3. Temperature change in NM-R following saline injection, 10mg/kg poly[i.c.] injection and 5mg/kg poly[i.c.] injection.

Results

Overall, we injected 18 animals with poly[i.c.] and measured the results 21 times using different methods and dosages. We found that the temperature change and seizure behavior was most evident with a 10mg/kg subcutaneous dose of poly[i.c.] when the animal was placed in a chamber with a ceramic heat emitter. While a 5mg/kg dose of poly[i.c.] produces a fever response, it was slower and less intense than the response induced by 10mg/kg.

We observed an increase in body temperature over a period of approximately four hours reaching as much as 9 degrees over the pre-injection temperature (Figure 3). We also observed stereotypical NM-R seizure behavior, such as head bobbing, teeth chattering and overall muscle contractions.

Conclusions

Poly[i.c.] elicits a fever response and increases temperature in the African naked mole-rat.

A fever induced by poly[i.c.] appears to elicit a seizure, but EEG confirmation is needed.

The long delay (over three hours) to raise temperature with the current procedure is inefficient. We are working to improve this method by injecting the animal at room temperature and moving to a warm chamber after the initial fever response develops.

The poly[i.c.-]induced febrile seizure in adult NM-R holds promise as a valuable new animal model in the study of epilepsy.