EFFECTS OF ALTERATIONS IN BODY TEMPERATURE ON PROPERTIES OF CONVULSIVE SEIZURES IN RATS

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It is well known that convulsive seizures may frequently be associated with acute febrile illnesses in early childhood, but less frequently in adult life (1, 2). Convulsions have also been reported to occur in patients subjected to fever therapy (3-5). In some epileptic subjects the frequency of seizures may be increased during fever, while in others the attack rate may be diminished (2). Experimentally, acute hyperpyrexia has been shown by Wegman (6) to cause convulsions in kittens. With regard to low body temperature, human refrigeration has been reported by Fay (7) to increase the excitability of the deep reflexes. Similarly, Barron and Matthews (8), and Ozorio De Almeida (9, 10) have shown that a reduction in body temperature of frogs increases the excitability of the spinal cord. In peripheral nerve Granit and Skoglund (11) have observed facilitation of ephaptic transmission, and Lorente de Nó (12) has shown that the rheobase is decreased when temperature is reduced.

Because of the paradoxical occurrence of febrile convulsions in some patients in contrast to febrile remission of seizures in others, it seemed important to analyze the effect of alterations in body temperature on various properties of experimental seizures without the complications, such as infection, dehydration, etc., which may attend febrile illness.

METHODS

Body temperature of Sprague-Dawley rats was altered by restraining the animals in circular wire mesh holders either in a refrigerator at a temperature of -8°C. or in an insulated heating cabinet at 55°C. until the desired rectal temperature was obtained. Rectal temperatures were determined with a mercury thermometer immediately before and after experimental seizures.

Electroshock seizures were produced by a 60-cycle alternating current apparatus designed by Dr. Lowell A. Woodbury; the current delivered is independent of the external resistance. Shocks were of 0.2 second duration, and were delivered through corneal electrodes. Minimal electroshock seizure thresholds (13) were compared at control and experimental body temperatures, with a period of at least 12 hours between tests for each animal. For observation of changes in pattern and duration of...
maximal seizures (14), supramaximal shocks of 150 mA. (or five times threshold) were given; the interval between tests was at least two hours.

To determine the effect of altered temperature on rate of recovery of maximal seizure pattern, groups of 4 to 12 rats were used at each desired body temperature. All were given a conditioning supramaximal shock, followed by a supramaximal test shock after the desired interval. The percentage of animals showing full recovery of seizure pattern, including the tonic extensor component, was noted. Percentage recoveries for various intervals were plotted on probit paper as a function of time, and

the resulting points fitted by eye to determine graphically the time for recovery of full seizure pattern in 50 per cent of the animals at each body temperature.

For determination of the rate of recovery of minimal seizure threshold, the method was the same except that an arbitrary value of 150 per cent of the unconditioned threshold at the same temperature was selected for the test shock.

Chemoshock seizure thresholds for intraperitoneally injected Metrazol or picrotoxin were determined by treating groups of four or more animals at each of several dose levels at each desired temperature and finding graphically (as above) that quantity of drug which would convulse 50 per cent of the animals at each temperature.

RESULTS

The minimal electroshock seizure threshold was found to vary directly with body temperature. When the logarithm of threshold was plotted against the reciprocal

Fig. 1. EFFECT OF BODY TEMPERATURE on the threshold for minimal electroshock seizures in rats. Electroshock threshold in mA. is plotted on a logarithmic scale (ordinate) as a function of the reciprocal of the absolute temperature (abscissa, top). For ease in interpretation the corresponding centigrade degrees are also shown (abscissa, bottom). Vertical broken line: normal body temperature (average of 21 rats); horizontal broken line: normal electroshock threshold (average of 159 rats). Each point along solid diagonal line represents one experiment.

Fig. 2. EFFECT OF BODY TEMPERATURE on the duration of maximal electroshock seizures in rats. Electroshock threshold in mA. is plotted on a logarithmic scale (ordinate) as a function of the reciprocal of the absolute temperature (abscissa, top). For ease in interpretation the corresponding centigrade degrees are also shown (abscissa, bottom). Vertical broken line: normal body temperature (average of 22 rats); horizontal broken line: total duration of maximal seizures at normal body temperature (average of 73 rats). Each point along solid diagonal line represents one experiment.
of the absolute temperature (fig. 1.), the data were approximately fitted by a straight line giving a $\mu$ value of 7500 calories per mole, corresponding to a $Q_{10}$ of 1.6.

The susceptibility to convulsions induced by picrotoxin or Metrazol was also increased by lowering the body temperature. The approximate $Q_{10}$ for picrotoxin was found to be 1.6, which is in agreement with the electroshock data. Occasional spontaneous seizures were observed when body temperature was elevated above $43^\circ C$. or reduced below $27^\circ C$. This would tend to compromise any observations taken beyond these limits.

The effect of body temperature on the total duration of maximal seizures is shown in figure 2. As might be expected the total duration varies inversely with the body temperature. The $Q_{10}$ was found to be 2.8 ($\mu$ value, 19,600 calories per mole). It is interesting to note that a sharp reduction in total seizure duration occurs when body temperature is reduced below $27^\circ C.$, as shown by the separate line in the upper right segment of figure 2. It should be mentioned that spontaneous convulsions were occasionally observed at and below this temperature.

Associated with the effect of variations in temperature on total seizure duration, changes in the relative duration of the various seizure components were observed. In general, a reduction in temperature decreased the fractional duration of the tonic phase and particularly the initial flexor component of the tonic phase. At elevated body temperatures the absolute as well as the relative duration of tonic flexion was increased; above $42^\circ C.$ the entire seizure tended to be a tonic flexion with superimposed fine clonus. It was difficult to measure the duration of the various components at temperatures below $27^\circ C.$ because the end-points were not clearly defined.

The effect of body temperature on the time for recovery of a full maximal seizure pattern following a supramaximal shock is shown in figure 3. It may be seen that the recovery time for 50 per cent of normal rats is $3.48 \pm 0.25$ minutes. When the body temperature was elevated to $40^\circ$ to $42^\circ C.$ the recovery time for 50 per cent of the animals was found to be $2.48 \pm 0.25$ minutes. Conversely when body temperature was reduced to $30^\circ C.$ it required $5.02 \pm 0.44$ minutes for 50 per cent of the animals to recover the maximal seizure pattern. Therefore the $Q_{10}$ between $30^\circ C.$ and $40^\circ C.$ is approximately 2 ($\mu$ value of 12,000 calories per mole) for recovery of the normal seizure pattern.

Following a maximal seizure, the rate of recovery of threshold was found to be doubled by a $10^\circ$ reduction in body temperature, giving a $Q_{10}$ of 2. This is in agreement with the results of the maximal shock experiments.
DISCUSSION

It is of interest to note that the temperature coefficients differ for seizure threshold, seizure duration and post-seizure recovery. This would seem to indicate a difference in the fundamental chemical processes underlying these three functions, but the identification of the specific temperature coefficients with particular limiting enzyme steps would be unwarranted.

Since seizure threshold was increased by a rise in body temperature, this factor alone might conceivably account for febrile remission of convulsive disorders in some patients. It obviously could not account for febrile onset of seizures in other cases. Spontaneous seizures were occasionally seen at high body temperatures in the present study, demonstrating that threshold is not the only factor determining the occurrence of convulsions.

SUMMARY

Characteristics of experimental seizures were studied in rats whose body temperatures were altered by exposure to extreme environmental temperatures. Seizure threshold was increased, seizure duration reduced and post-seizure recovery hastened by increased body temperature, and conversely changed by decreased body temperature. The data were adequately fitted by plotting the logarithm of each function against the reciprocal of absolute body temperature. For seizure threshold the $Q_{10}$ was found to be 1.6, for seizure duration 2.8 and for recovery 2.0. The possible significance of the findings is briefly discussed.

REFERENCES