11599

Effects of Body Temperature and of Pentobarbital on Brain Damage Produced by Insulin Shock.*

DAVID B. TYLER. (Introduced by C. H. Thienes)

From the Department of Pharmacology, School of Medicine, University of Southern California.

In most animals there is a fall in body temperature during insulin shock. This fall has been attributed to the lack of available glucose which is essential for the shivering mechanism.[1, 2] In cats, the fall in temperature is very pronounced and, as a rule, drops to about 8° to 10° C above that of the room. It was previously shown[3] that it was necessary to maintain cats in the "medullary phase" (Phase IV) of insulin shock for at least 100 minutes in order to produce irreversible clinical signs of brain damage. In those experiments, the body temperature of the animals ranged from 28° to 33°, representing a drop of 6° to 11° below normal.

During these experiments, it appeared that brain damage occurred earlier in animals resistant to the hypothermic action of insulin. The following experiments were carried out to test this matter further. Some observations on the results obtained from administering sodium pentobarbital (nembutal) during insulin shock are also reported.

Method. Cats fasted 18 hours were given 15 to 20 u/kg of insulin. Fifteen minute records of the neurological state of the animal were made until the animal reached Phase IV, (as described by Frostig.[4] It was then closely watched and when it showed signs of circulatory collapse and extreme respiratory irregularities, small amounts of glucose were given intraperitoneally. This usually restored the animals temporarily to Phase II or III. This glucose administration was repeated again whenever necessary. The body temperature (rectal) in the "warm" cats was maintained at near normal levels either by a hot pad or by working at room temperature of about 30° C. Hypoglycemia was finally terminated with glucose. Those cats which showed irreversible clinical symptoms of cortical or cerebral damage[3, 5] were considered as having brain

* We are indebted to Eli Lilly Company for the insulin and to Abbott Laboratories for the sodium pentobarbital (nembutal) used in these experiments.

1 Dworkin, S., and Finney, W. H., *Am. J. Physiol.*, 1927, **80**, 75.

2 Tyler, D. B., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 278.

3 Tyler, D. B., and Ziskind, E., PROC. SOC. EXP. BIOL. AND MED., 1940, **44**, 622.

4 Frostig, J. P., *Arch. Neurol. and Psychiat.*, 1938, **39**, 219.

5 Ziskind, E., and Tyler, D. B., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 734.

damage. Histological data will be presented at a later date.

Results. In the table the results obtained in animals with near normal body temperature were compared with those obtained in animals where the temperature was allowed to fall. The duration of Phase IV is listed in Column I, the temperature range during this period in Column II, the incidence of brain damage in Column III, and the degree of brain damage (+=cortical, ++=cortical plus subcortical, +++=clinical picture of decerebration) in Column IV. It can be seen that when the body temperature was prevented from falling, not only the incidence of brain damage in each group was higher, but the degree of damage produced was greater. In 8 "cool" cats, no damage occurred up to 45 minutes. Of the 5 "warm" cats, 2 terminated after 15 minutes in the medullary phase showed no clinical evidence of brain damage, 3 terminated at 25, 35 and 45 minutes all showed evidence of cortical damage. For periods above 45 minutes, brain damage invariably resulted when the body temperature was kept at normal levels.

In another series of experiments, 10 cats were given sodium pentobarbital (10 mg/kg) when the first myoclonic jerk or convulsion occurred. The administration of this drug abolished the characteristic progression of the symptoms described by Frostig, and the only indications of the cats reaching the medullary phase were by the occurrence of extremely slow pulse and very irregular respiration. Of these animals, 4 died very shortly after the administration of nembutal, confirming the observation of Yannet[6] that animals under this drug are more sensitive to insulin. Six of the cats were observed as described above, glucose being given when the pulse or respiration warranted it. When they had spent a total of 150 minutes in the medullary phase, the hypoglycemia was terminated. All 6 cats, however, remained in a prolonged coma 4 to 6 days in spite of the fact that the hypoglycemia was terminated. Three died

TABLE I.

No. of animals	I Minutes in phase IV	II Temperature range, °C	III Incidence of brain damage	IV Degree of brain damage
8	0-45	31-34	0	0
5	0-45	36-39	60	+
7	46-90	31-34	28	+
5	46-90	36-39	100	++½
8	91-120	31-33	63	++
8	91-120	36-38	100	+++

[6] Yannet, H., *Arch. Neurol. and Psychiat.*, 1939, **42**, 395.

on the 4th and 5th days without regaining consciousness. Two of the remaining 3 cats recovered and showed no clinical symptoms of brain damage. The other one recovered with indications of some cortical damage. These preliminary results seem to indicate that sodium pentobarbital, although increasing the sensitivity to insulin, exerts some protection to the brain. In other experiments where sodium pentobarbital was not administered, 150 minutes in the medullary phase usually produced severe cortical and subcortical damage, and the resulting preparations lived about 48 hours.

Discussion and Conclusions. The protective action of cooling during insulin shock has been reported previously.[2] These experiments demonstrate that when the body temperature is prevented from falling, the time necessary to produce damage is considerably shortened, and the degree of brain damage is greater. This is to be expected since the higher the temperature, the higher the metabolic rate and the greater the oxygen need of the brain. When the body temperature is kept at normal levels during insulin shock it would seem that a relatively greater degree of tissue anoxia results than when the body temperature is permitted to fall, due to the greater need of oxygen at higher temperatures. This may be a factor responsible for the prolonged comas and accidents frequently occurring during insulin shock therapy, since the drop in body temperature in humans is not as great as that which occurs in cats. Dogs also are found to be resistant to the hypothermic action of insulin. In this laboratory, it has been found that considerably shorter periods are necessary to produce brain damage in this animal than is needed for cats. In fact, brain damage has been produced in the dog without it showing the characteristic symptoms of the 4th phase.[7]

At this time, no explanation can be offered for the prolonged post hypoglycemic coma which results when sodium pentobarbital is administered to insulinized cats, except perhaps for the known reduction of metabolic rate.[8]

---

[7] Katz, Y., private communication.

[8] Zorn, C. M., Muntwyler, E., and Barlow, O. W., *J. Pharm. and Exp. Therap.*, 1939, **66**, 326.