11548

Relationship Between Insulin Dosage, Duration and Degree of Hypoglycemia and Production of Brain Damage.*†

DAVID B. TYLER AND EUGENE ZISKIND. (Introduced by D. R. Drury.)

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

This report deals with the relation of insulin dosage, duration and degree of the ensuing hypoglycemia, and the resulting brain damage produced. Observations of a paradoxical reaction with insulin are also recorded.

It is well established from the work of Scott and Dotti,[1] Zucker and Berg,[2] and many others, that from 20 to 60 minutes after the injection of insulin, the blood sugar reaches its lowest level and remains there with minor fluctuations for a period depending upon the amount of insulin given. With insulin doses such as we used, of from 10 to 20 units per kilo of bodyweight, the hypoglycemia persists from 10 to more than 24 hours. However, independent of the hypoglycemia certain clinical symptoms occur which indicate a progressive loss of function, in a phylogenetic order, from the higher cortical areas to the lower or medullary centers.[3-6] In this connection, Frostig[4] described 4 stages of hypoglycemia in man after large doses of insulin, based on impairment of the function of (1) cerebral cortex, (2) basal ganglia and thalamus, (3) midbrain, and (4) medulla. In our previous report,[7] certain interesting data became apparent bearing on the problem of insulin dosage in relation to brain damage.

The method used has been described in a previous report.[7] Briefly stated, doses of insulin were given subcutaneously to cats fasted 18 hours and not previously treated with insulin. Complete

* Insulin was kindly furnished by Eli Lilly & Co.

† We are indebted to Dr. C. H. Thienes of the Department of Pharmacology for the use of laboratory space and many helpful suggestions.

1 Scott, E. L., and Dotti, L. B., *Arch. Int. Med.*, 1932, **50**, 511.

2 Zucker, T. F., and Berg, B. N., *Am. J. Physiol.*, 1937, **119**, 531.

3 Angyal, L. V., *Z. Neur. and Psychiat.*, 1937, **157**, 35.

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

5 Himwich, H. E., Frostig, J. P., Fazekas, J. F., and Hadidian, Z., *Am. J. Psychiat.*, 1939, **96**, 371.

6 Ziskind, E., and Tyler, D. B., in preparation.

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

quarter-hour notations of the neurological state of the animal were made. When the animal showed signs of critical medullary decompensation, small amounts of glucose (100-200 mg) were given intraperitoneally as needed, in order to restore the circulation, pulse and respiration, but still maintain a severe hypoglycemia. The hypoglycemia was terminated after 9 to 20 hours with glucose. We considered those animals had brain damage which showed the irreversible clinical symptoms of "decortication" and "decerebration" described elsewhere.[7] In this report when we describe a "stage" of hypoglycemia such as the "medullary stage," we refer to the neurological symptoms at that time.

1. *The Relation Between Insulin Dose and Incidence of Brain Damage.* Column III of Table I shows that the greater the dosage the greater the incidence of residual brain damage. In animals receiving 10, 15 and 20 units of insulin per kilo, the incidence of brain damage was respectively 30%, 33%, and 62%. These results cannot be correlated with the duration of hypoglycemia or the period of coma (columns IV and V). These findings correspond to those previously reported by Yannet.[8]

TABLE I.

I Insulin dose	II Time before myoclonic jerks	III Incidence of residual brain damage	IV Hr of hypoglycemia	V Hr coma
20 u./kg	4.16 (20)	62% (13)	11	7
15 u./kg	3.67 (43)	33% (33)	13	9
10 u./kg	3.28 (20)	30% (20)	7.5	4.5
Less than 5 u./kg	2.24 (12)	—	—	—

Number in parenthesis indicates number of animals.

2. *The Relation of Duration of Medullary Stage to Brain Damage.* Residual brain damage did not occur in our series irrespective of the dose of insulin unless the animal was in the "medullary stage" for not less than 100 minutes. This medullary stage (Stage IV of Frostig) is characterized by pin point pupils, bradycardia, respiratory irregularities especially Cheynes-Stokes respiration, flaccidity, and finally symptoms of circulatory collapse. However, the time that the animal must be kept in this stage to produce brain damage varies indirectly with the body temperature of the animal. These findings do not lend support to the thesis that insulin *per se* is toxic to the brain cell.

3. *Paradoxical Relation of Increasing Dose of Insulin and Disappearance of Cerebral Functions.* The larger the dose of insulin

[8] Yannet, H., *Arch. Neur. and Psychiat.*, 1939, **42**, 395

(within the limits of our experiments) the longer the latent period before cortical functions disappear, as gauged by the loss of consciousness and the time of appearance of the first myoclonic jerks. (Column II of table.) The average time of appearance of the first myoclonic jerks in cats receiving 5 u/kg or less was 2.24 hours, 10 u/kg 3.28 hours, 15 u/kg 3.67 hours, and 20 u/kg 4.16 hours. We are unable to suggest the reason for this reaction.

Conclusions. 1. The larger the dose of insulin the greater the incidence of brain damage. However, irrespective of the insulin dose, brain damage did not occur in our animals unless they were kept in the "medullary stage" of hypoglycemia for at least 100 minutes. 2. In cats, not previously treated with insulin, the larger the dose the longer time it took for the appearance of neurologic signs of hypoglycemia.

11549 P

Elimination of Metrazol.

J. M. DILLE AND VICTOR P. SEEBERG

From the Department of Pharmacology, College of Pharmacy, University of Washington, Seattle, Washington.

Pharmacological and clinical evidence points to the fact that metrazol is very rapidly detoxicated in the body. The intravenous administration of a convulsive dose produces typical clonic convulsions from which the animal rapidly recovers.

There is a possibility that the metrazol might be excreted by the kidneys, and so our first step consisted in eliminating this possibility. Chemical analysis of the urine of cats receiving convulsive doses of metrazol showed none of the drug to be present in the urine. Bilaterally nephrectomized cats showed the same reaction to a convulsive dose of metrazol as they did before the performance of the nephrectomy. Hinsberg has shown that practically no metrazol is excreted by the intestinal route. It therefore seems logical that metrazol is not excreted but is detoxified.

The liver has generally been assumed to be the locale for drug detoxication. We therefore administered phosphorus to cats. Cats treated in this way died from the administration of a dose of metrazol which formerly produced only slight convulsions. The role of the liver was further tested by a comparison of the dose required to