CHEMICAL CHANGES IN CEREBRAL CORTEX FOLLOWING LOCAL THERMOCOAGULATION AND LOCAL FREEZING*

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The sequelae of an injury to the cerebral cortex may at times depend on the nature of the agent producing the trauma. Thus, local freezing of the cerebral cortices of cats, dogs, and monkeys profoundly disturbs the electrical activity of their brains[6] and, as Openchowski[7] and Speransky[8] have amply demonstrated, dogs treated in this manner may develop severe convulsive seizures. In contrast, convulsions have not been observed following local thermocoagulation[1] of corresponding areas in monkeys. Dusser de Barenne and his associates[3] have shown that these two methods of producing local insult have quite different effects on the acidity of the injured areas; hence, different chemical states must have been induced in the cortex by the two procedures. It seemed possible, therefore, that a comparison of the chemical analyses of brains injured in the two different ways might explain the pH shifts and might also throw some light on the chemistry of the preconvulsive state. Chemical analyses of injured brains were made and the results are reported here.

Procedures

Cats anesthetized with nembutal were used. The cerebral hemispheres were exposed, and electrodes for the measurement of pH and electrical activity were adjusted on the surface of the brain. After a preliminary period of observation, a portion of one hemisphere was superficially frozen with an ethyl chloride spray for one minute, or thermocoagulated at 80° for six seconds according to the method of Dusser de Barenne.[2] Thirty to sixty minutes later, after further observations of the pH and electrical activity had been made, both hemispheres were frozen simultaneously *in situ* with liquid air. The frozen cortex was removed and kept in liquid air until analyzed. Complete details of the apparatus used and of the chemical methods employed have been given in previous publications.[5, 9]

Results

Thermocoagulation of the cerebral cortex led to a prompt obliteration of the electrical activity of the thermocoagulated area.

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There was no tendency for the electrical activity to return during the period of observation. The pH of the injured region showed a profound and lasting decrease. The concentrations of lactic acid and inorganic phosphate were significantly higher, while those of phosphocreatine and "hexose phosphates" were considerably lower in the heat-treated area than were the respective concentrations in an untreated area. Table 1 summarizes the results.

TABLE 1

EFFECT OF LOCAL THERMOCOAGULATION ON CORTICAL pH AND ON CONCENTRATIONS OF LACTIC ACID AND CERTAIN PHOSPHATE FRACTIONS

Hemisphere	*pH*		*Lactic acid*	*Inorg. phos.*	*Phospho-creat.*	*Pyro-phos.*	*Hexose phos.*
	Before thermocoagulation (T. C.) of one hemisphere	*After thermocoagulation (T. C.) of one hemisphere*					
			mg./100 gm.	mg. P/ 100 gm.	mg. P/ 100 gm.	mg. P/ 100 gm.	mg. P/ 100 gm.
Normal	7.08	7.18	16.3	12.2	14.6	15.6	21.6
T. C.	7.14	6.78	89	22.3	8.3	16.3	15.3
Normal	7.25	7.24	52	11.3	11.0	19.1	24.2
T. C.	7.15	6.83	205	29.7	3.1	14.4	17.4
Normal	7.14	7.19	8.9	8.4	13.4	15.4	24.6
T. C.	7.12	6.62	113	25.2	4.1	14.0	18.5

Superficial freezing of the cerebral cortex was followed by electrical silence, but as the tissue warmed up, there was a partial return of electrical activity. The observed pH of the areas studied in these cats was not greatly changed by freezing. In this respect they differed from the monkeys previously studied[3] where a distinct alkaline shift was observed in the frozen areas.

The concentrations of the various chemical fractions of the frozen tissue as well as of those of control areas are summarized in Table 2. A comparison of the results obtained for the thermocoagulated tissue with those for frozen tissue indicates that while the direction of change in the concentrations of the chemical substances is the same, the effects are quantitatively greater following thermocoagulation.

Discussion

The chemical findings give no clear explanation of the tendency for convulsions to appear after one type of insult and not after the

TABLE 2

EFFECT OF LOCAL FREEZING AND THAWING ON CORTICAL pH AND ON CONCENTRATIONS OF LACTIC ACID AND CERTAIN PHOSPHATE FRACTIONS

Hemisphere	*pH*		*Lactic acid*	*Inorg. phos.*	*Phospho-creat.*	*Pyro-phos.*	*Hexose phos.*
	Before freezing of one hemisphere	*After thawing*	mg./100 gm.	mg. P/ 100 gm.	mg. P/ 100 gm.	mg. P/ 100 gm.	mg. P/ 100 gm.
Normal	6.99	6.98	20.3	11.9	11.3	22.4	25.2
Frozen	6.97	7.28	65.5	15.0	9.9	23.0	22.9
Normal	7.23	7.23	13.5	11.5	13.5	21.1	22.2
Frozen	7.19	7.21	44.7	13.1	7.8	15.5	18.5
Normal	7.34	7.37	23.3	10.5	11.3	19.9	27.1
Frozen	7.29	7.32	44.6	11.9	10.1	16.2	22.3

other, but certain suggestions may be drawn from the evidence. After thermocoagulation the changes are much greater in magnitude than is the case after freezing, and it may be that the cells are so severely altered by the treatment with high temperatures that they are unable to function at all. Furthermore, after thermocoagulation some cellular enzymes may have been denatured by the high temperatures to which they have been subjected, while after freezing, although cell walls may have been ruptured, these enzymes were probably intact. It is possible then that these displaced chemical constituents might have been responsible for the consequent electrical dysrhythmias because of their action on other intact or partially injured cells.

On the basis of some simple calculations, the increase in concentration of lactic acid following thermocoagulation, though large, seems insufficient to account for the great decrease in the observed pH. An increase in carbon dioxide tension could perhaps explain the acidity shift, but this seems unlikely in view of the fact that vasodilation was observed in the injured region. It appears probable, therefore, that some unidentified acidifying substance was produced.

The findings with respect to pH in the freezing experiments are also difficult to explain, for the alkalinity sometimes observed and the neutralization of the formed lactic acid are still to be accounted

for. The amount of base released by the breakdown of phosphocreatine and hexose phosphate is too small to be of much significance. A local decrease in carbon dioxide production or a local increase in blood flow may be the unconsidered variable, and the possibility remains that an unknown alkaline substance was produced by the procedure.

Summary

Local thermocoagulation and local freezing of the cerebral cortex produce increased concentrations of lactic acid and inorganic phosphate and decreased concentrations of phosphocreatine and hexose phosphates in the injured areas. The quantitative changes in chemistry are much greater in a thermocoagulated area than in a frozen area.

The suggestion is made that freezing does not kill all of the cortical cells and that the subsequent altered electrical state is due to cells functioning in an abnormal chemical environment.

REFERENCES

1 Dusser de Barenne, J. G.: The disturbance after laminar thermocoagulation of the motor cerebral cortex. Brain, 1934, *57*, 517-26.

2 Dusser de Barenne, J. G.: The method of laminar thermocoagulation of the cerebral cortex. Yale J. Biol. & Med., 1938, *10*, 573-76.

3 Dusser de Barenne, J. G., Marshall, Clyde, McCulloch, W. S., and Nims, Leslie F.: Observations on the pH of the arterial blood, the pH and the electrical activity of the cerebral cortex. Am. J. Physiol., 1938, *124*, 631-36.

4 Dusser de Barenne, J. G., and McCulloch, W. S.: Some effects of laminar thermocoagulation upon the local action potentials of the cerebral cortex of the monkey. Am. J. Physiol., 1936, *114*, 692-94.

5 Nims, Leslie F.: Glass electrodes and apparatus for the direct recording of pH in vivo. Yale J. Biol. & Med., 1938, *10*, 241-46.

6 Nims, Leslie F., Marshall, Clyde, and Neilsen, Aage: Effect of local freezing on the electrical activity of the cerebral cortex. Yale J. Biol. & Med., 1941, *13*, 477.

7 Openchowski: Sur l'action localisée du froid, appliqué a la surface de la région corticale du cerveau. Compt. rend. Soc. de biol., 1883, *35*, 38-43.

8 Speransky, A. D.: *A basis for the theory of medicine.* International Publishers, New York, 1935.

9 Stone, W. E.: Acid-soluble phosphorus compounds and lactic acid in the brain. J. Biol. Chem., 1940, *135*, 43-50.

We wish to express our appreciation for the aid and encouragement received from the late Professor J. G. Dusser de Barenne, in whose laboratory this work was done.