

THE EFFECT OF VARIOUS ORGANS ON THE ACETONE CONTENT OF THE BLOOD IN PHLORHIZIN AND PANCREATIC DIABETES

BY HAROLD E. HIMWICH, W. GOLDFARB, AND A. WELLER

(From the Department of Physiology, Yale University, New Haven)

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Inasmuch as the accumulation of acetone bodies in the blood of a diabetic animal may exert a toxic influence, the study of acetone metabolism has been the subject of numerous investigations. The early observations made on surviving organs indicated that the perfusion of the liver with the amino acids, leucine, phenylalanine, or tyrosine caused an increased acetone content of the perfusate (Embden, Salomon, and Schmidt, 1906; Embden and Oppenheimer, 1912; Masuda, 1912; Loeb, 1914). That the liver was the only source of acetone bodies was concluded from experiments on excised tissue which was perfused with the animal's own blood (Almagia and Embden, 1905; Embden and Kalberlah, 1906). The conversion of part of the β -hydroxybutyric acid of the perfusing fluid of the liver to acetoacetic acid was noted by Snapper and Grünbaum (1927). However, neither compound was oxidized in the liver. Acetoacetic acid injected into normal and depancreatized dogs remained longer in the blood of the depancreatized animals despite the fact that the muscles of both types of experimental animals utilized acetone with equal facility (Chaikoff and Soskin, 1928-29). The authors concluded that the liver of the depancreatized dog produced acetone bodies. In the present study of phlorhizinized and depancreatized dogs an attempt was made to determine the effects of the various organs by analyses of samples of their afferent and efferent blood for acetone bodies.

Method

The operative procedures and methods of sampling the blood entering and leaving organs have been described in other papers

from these laboratories (Himwich, Koskoff, and Nahum, 1929-30; Himwich, Chambers, Koskoff, and Nahum, 1931). The viscera investigated were liver, muscle, kidney, and the organs drained by the portal vein. Blood was drawn from the depancreatized dogs 48 or 72 hours after the operation, and from the phlorhizinized dogs after the appearance of definite amounts of acetone in the urine. 64 observations were obtained on six phlorhizinized dogs, and 76 on twelve depancreatized dogs. The urine of three depancreatized dogs collected for 24 hours was analyzed for acetone bodies. Acetone determinations of blood and urine were made by the method of Van Slyke and Fitz (1917) and the error of a single determination was ± 0.8 mg. per cent.

TABLE I
Acetone Content of Blood of Phlorhizinized and Depancreatized Dogs

	Dog No.	Hepatic vein	Portal vein	Femoral artery	Femoral vein
		<i>mg. per cent</i>	<i>mg. per cent</i>	<i>mg. per cent</i>	<i>mg. per cent</i>
Phlorhizinized dogs	1	40	43	34	40
	2	46	34	14	22
	3	38	29	32	25
Depancreatized dogs	4	13	4	8	4
	5	26	5	5	18
	6	35	17	28	25

Results

The data from six dogs are presented in Table I to illustrate the effects of the various organs on the acetone content of the blood. The afferent blood supply of the liver has been calculated from the ratio of Burton-Opitz (1911), who found that 0.3 comes from the hepatic artery, and 0.7 from the portal vein. Table II contains a summary of the number of experiments in which each of the organs either added, or made no change, or removed acetone from the blood. Differences exceeding 3 times the experimental error were taken as significant.

A consideration of Tables I and II shows that there is a considerable variation in the effects of the organs investigated on the acetone content of the blood. As a rule the liver added acetone, but the results on muscle and the organs drained by the portal

vein were not so consistent. The liver added acetone bodies to the blood twenty-seven times and removed them twice. Of the twenty-three observations on muscle in which the change was greater than 3 times the experimental error, acetone was removed in twelve instances, and liberated in eleven others. The organs draining into the portal vein absorbed acetone in twelve of the nineteen significant experiments. In five of the experiments on the phlorhizinized dogs all the organs were producing acetone bodies.

TABLE II

Summary of Effects of Muscle, Liver, and Organs Drained by Portal Vein on Blood Acetone

	Muscle			Liver			Portal organs		
	Added	No change	Removed	Added	No change	Removed	Added	No change	Removed
Phlorhizinized dogs	5	5	6	11	3	2	7	5	4
Depancreatized dogs	6	5	6	16	1	0	0	9	8
Total	11	10	12	27	4	2	7	14	12

The readings are for the number of experiments in which acetone was added to, remained unchanged, or was removed from the blood.

DISCUSSION

Though the data here reported were obtained on organs studied *in situ*, they agree, in part, with the results gained by the perfusion of surviving organs. They are also in accord with the observations of Chaikoff and Soskin (1928-29) who injected acetoacetic acid intravenously, for the liver was found to be the chief source of acetone bodies. However, the present work differs from previous investigations since some experiments showed that other organs may also produce acetone bodies. This conclusion is evident from the summary of the data in Table III. In Column 2 there is listed the number of experiments in which muscle added, made no change, or removed acetone from the blood. The effects of the other organs in each set of experiments listed in Column 2 are noted in Columns 3 to 8.

It may be seen (Table III) that the liver usually added acetone, and did so regardless of the action of the other organs, which liberated acetone bodies in only eighteen of the forty-two significant observations. The organs drained by the portal vein and muscle exhibited a similarity in reaction. In the eleven experiments in which muscle added acetone, five of the seven significant results showed that the organs drained by the portal vein were also adding that substance. Similarly, in the twelve experiments in which muscle was found to remove acetone, the organs drained by the portal vein removed acetone nine times and added it only once. Differences between the femoral artery and vein were found to be within 3 times the experimental error in ten cases; in eight

TABLE III
Correlation of Changes of Blood Acetone Produced by Muscle with Those of Liver and Organs Drained by Portal Vein

Muscle		Liver			Portal organs		
(1)	(2)	Added (3)	No change (4)	Re- moved (5)	Added (6)	No change (7)	Re- moved (8)
Added	11	10	1	0	5	4	2
No change	10	9	0	1	1	8	1
Removed	12	8	3	1	1	2	9

The readings are for the number of experiments in which acetone was added to, remained unchanged, or was removed from the blood.

of these, differences between the femoral artery and portal vein were also within 3 times the experimental error.

We have calculated that if the liver weight is equal to 2.7 per cent of the body weight (Junkersdorf, 1925) and its blood flow 84 cc. per 100 gm. of tissue per minute (Burton-Opitz, 1911), the amount of acetone that could be produced by the livers of the twelve depancreatized dogs varied from 12 to 100 gm. per day. In three of the experiments in which the urinary acetone was determined, the excretion was less than 1 gm. per day. Since the maximum possible excretion of acetone through the lungs was found by Widmark (1920) and Higgins (1920) to be less than 3 gm. per day, it is evident that the other organs must have removed the acetone from the blood. Chaikoff and Soskin (1928-29) have demon-

strated that storage could not account for the acetone thus removed, and concluded that the organs must have oxidized it. That the liver is more prone to ketosis may be explained by the observations of Hunt and Bright (1926), who found that the metabolic rate of the liver per 100 gm. of tissue was approximately 20 times that of muscle and 10 times that of the other viscera.

Woodyatt (1921) and Shaffer (1921, 1922) have shown that acetone bodies are not produced by an animal until the keto-antiketogenic ratio exceeds 1. Their results have been based on observations on the entire animal, and the criterion of ketosis has been the appearance of acetone in the urine. From the present experiments it is evident that the excretion of acetone bodies by the organism is the algebraic sum of the effects of all the organs. Only when all the organs are liberating acetone bodies are the amounts excreted through the lungs and kidneys the sum of the acetone bodies produced by the entire organism.

The femoral artery was found to have a higher acetone content than the hepatic vein in five of the thirty-three experiments. This indicates that there may be some other source of acetone bodies than the organs studied.

SUMMARY AND CONCLUSION

The acetone metabolism of organs *in situ* was studied in twelve depancreatized and six phlorhizinized dogs. The liver was found to be the chief site of acetone production (twenty-seven of twenty-nine experiments); while muscle and the organs drained by the portal vein liberated acetone bodies in eighteen experiments, and removed that substance in twenty-four others. These results indicate that the acetone excretion by the kidney and lungs is the algebraic sum of the actions of the various organs.

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