Effects of Tolbutamide on Cardiovascular Function and Myocardial Metabolism of Intact Dogs.* (26629)

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The effects of tolbutamide on peripheral glucose utilization and on hepatic glucose output have been investigated extensively, but remain subjects of considerable controversy(1,2). Interpretation of much of the data is limited by lack of information on rates of blood flow in conjunction with measurement of glucose arteriovenous differences (3) and by certain assumptions in radioactive tracer methods(4). Technics developed to study myocardial metabolism in the intact dog are free of these disadvantages and have been applied in the present work to elucidate the action of tolbutamide on the heart.

Materials and methods. The experimental model employed has been described in detail (5). Eight well-nourished mongrel dogs were deprived of food but not of water overnight, (approximately 18 hours). They were then anesthetized with morphine, 3 mg/kg, subcutaneously, followed in 30 minutes by a 50/50 mixture of Nembutal and Dial-urethane,† 0.25 cc/kg, intravenously. The trachea was intubated and the coronary sinus, aorta and inferior vena cava were catheterized *via* a jugular vein, femoral artery and femoral vein respectively. During catheterization the animals were given heparin, 5 mg/kg, intravenously, aqueous penicillin, 100,000 units, and streptomycin, 1 g, intramuscularly.

The following were determined: cardiac output (Fick principle with O_2); coronary blood flow (nitrous oxide desaturation method); aortic and coronary sinus whole blood concentrations of glucose, pyruvate, lactate, O_2 and CO_2; aortic and coronary sinus plasma concentrations of Na^+ and K^+; and aortic blood pH. Systemic blood pressure was registered on a water manometer connected to the femoral artery catheter. Heart rate was determined on electrocardiograms recorded with a Sanborn Viso-Cardiette.

Immediately after the blood samples and recordings were obtained, tolbutamide (Orinase),† 40 mg/kg, was injected rapidly into the femoral vein catheter. One hour later the sampling and recording were repeated. This interval was selected because preliminary observations revealed that the maximal change in the arterial blood glucose concentration was usually affected by this time. All animals recovered from the experiments.

Results. Significantly decreased arterial blood concentrations of glucose developed by one hour after tolbutamide administration (Table I). Despite this fall, myocardial extraction (coronary arteriovenous difference) and utilization (coronary arteriovenous difference $\times$ coronary blood flow) of glucose were fully maintained. This continued ability of the myocardium to obtain glucose in undiminished amounts at the lowered arterial concentrations is shown by the striking elevation of the percent extraction of glucose (coronary arteriovenous difference/arterial concentration $\times$ 100). No significant modifications were produced by tolbutamide in the arterial concentrations and myocardial usage of pyruvate and lactate. Arterial concentrations of Na^+ (control 148.3 $\pm$ 1.0 mEq/l, treated 150.1 $\pm$ 1.4 mEq/l) and of K^+ (control 4.3 $\pm$ .2 mEq/l, treated 4.4 $\pm$ .3 mEq/l) did not change significantly, and neither before nor after tolbutamide administration was there a significant coronary arteriovenous difference of these substances.

Oxygen concentration and saturation of the arterial blood remained stable and there was no significant change in oxygen con-

* Supported by grants from Cleveland Area Heart Soc. and U. S. Public Health Service.

† The Dial-urethane was generously contributed by Ciba Pharmaceutical Products, Inc., Summit, N. J., and tolbutamide (Orinase) by Upjohn Co., Kalamazoo, Mich.

TABLE I. Metabolic Findings Before (Control) and One Hour After (Treated) Administration of Tolbutamide (Mean ± S. E. of Mean).

		Arterial concentration, mg (or vol) %	Myocardial extraction,* mg (or vol) %	% extraction†	Myocardial utilization,‡ mg (or vol)/100 g/min.
Glucose	Control	74.1 ± 2.3	10.6 ± 1.6	14.5 ± 2.3	9.4 ± 1.4
	Treated	51.6 ± 4.5 §	14.0 ± 1.9	26.9 ± 2.6§	11.4 ± 1.7
Pyruvate	Control	1.10 ± .12	.58 ± .10	50.6 ± 4.1	.52 ± .10
	Treated	1.12 ± .09	.72 ± .06	65.3 ± 4.1	.58 ± .04
Lactate	Control	8.0 ± 1.1	3.6 ± .7	43.6 ± 4.7	3.1 ± .6
	Treated	10.0 ± 1.1	4.9 ± .6	50.7 ± 4.4	4.1 ± .6
Oxygen	Control	19.1 ± .4	12.5 ± .6	66.3 ± 3.3	11.3 ± .7
	Treated	20.2 ± .5	14.5 ± .6	71.7 ± 3.0	11.7 ± .5

* Coronary arteriovenous difference.
† Coronary arteriovenous difference/arterial concentration × 100.
‡ Coronary arteriovenous difference × coronary blood flow.
§ Indicates a significant difference from control value ($p < .01$).

sumption by the heart or in its respiratory quotient (.84 ± .06 to .91 ± .03). Although arterial carbon dioxide content decreased (45.2 ± .9 to 41.3 ± 1.2 volumes %) ($p < .05 > .01$), arterial pH was not affected (7.20 ± .01 to 7.23 ± .08).

No significant alterations occurred in the cardiovascular dynamics under investigation (Table II).

Discussion. During tolbutamide-induced hypoglycemia in the intact, anesthetized dog, the heart was capable of extracting blood glucose in amounts equivalent to those obtained during the normoglycemic state. This ability is expressed by the significantly increased percent extraction of glucose. In contrast, depression of arterial glucose concentration to comparable levels by starvation(5) or by diphtheria toxin is associated with a marked reduction in glucose extraction by the myocardium. These observations may be construed to indicate that tolbutamide, directly or otherwise, facilitates the passage of glucose from the blood into the myocardial cell even when the concentration of arterial glucose is diminished.

TABLE II. Hemodynamic Findings Before (Control) and One Hour After (Treated) Administration of Tolbutamide (Mean ± S.E. of Mean).

	Control	Treated
Aortic blood pressure, mm Hg	116.5 ± 4.2	120.9 ± 4.0
Heart rate, beats/min.	63.1 ± 4.0	83.1 ±11.4
Coronary blood flow, ml/100 g/min.	89.0 ± 2.4	81.0 ± 3.4
Cardiac index, l/meters²/min.	2.6 ± .4	2.3 ± .3
Left ventricular work, kg meters/min.	3.9 ± 1.0	3.5 ± .5
Left ventricular efficiency, %	15.0 ± 3.2	12.3 ± 1.7
Peripheral vascular resistance (arbitrary units)	2.61± .30	3.22± .55
Coronary vascular resistance (arbitrary units)	78.9 ± 3.6	91.0 ± 5.5

Note: There are no statistically significant differences between control and treated groups.

That tolbutamide increases peripheral utilization of glucose has been asserted(6,7) but also denied(8,9). Under the conditions prevailing in our dogs, the myocardium maintained but did not increase its usage of glucose. It has been demonstrated that the amount of glucose extracted by the heart is directly related to arterial glucose concentrations at values exceeding the myocardial threshold(5). Even when entrance of glucose into the cell is expedited by tolbutamide, the availability of the substrate may be pertinent in determining the degree of its utilization. In contrast to its effects upon the metabolism of glucose, tolbutamide failed to influence significantly that of the other substrates which were studied.

Numerous investigations have indicated that the metabolic activities of tolbutamide are consequent to the release of endogenous

insulin(10,11,12,13). This conclusion is also supported by the notable similarity of the effects of tolbutamide to those of injected insulin(14) upon cardiac carbohydrate metabolism.

Summary. Tolbutamide, 40 mg/kg, was rapidly administered into the femoral vein of intact, anesthetized dogs, deprived of food overnight. One hour later the following were observed: a) a significant decrease in arterial concentration of glucose; b) a significant elevation in *percent* of blood glucose extracted by the myocardium without any significant change in *absolute* amount extracted or *total* amount utilized; c) no significant change in arterial concentration or myocardial extraction and utilization of pyruvate, lactate, oxygen, Na^+ or K^+; d) no significant deviation in cardiovascular dynamics including coronary blood flow and cardiac index.

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Received March 10, 1961. P.S.E.B.M., 1961, v107.

Changes in Phosphorus Metabolism of the Gastrocnemius Muscle in Aging White Rats.* (26630)

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In pursuit of evidence for the corollary to Sumner's classical statement(1) that "life is an orderly function of enzymes" *viz.* that senescence in structures exhibiting anatomical and functional decline with age should be reflected by corresponding alterations in activity of significant cell catalysts, a long-range study has been under way in this laboratory of the changes in enzymes related to metabolism of high-energy organophosphorus compounds in skeletal muscle of aging rats. Potter, *et al.*(2) reported a marked rise in adenosine triphosphatase (ATP-ase) activity in the skeletal muscle of the immediately postpartum rat. Moog(3) and Robinson(4) in developing chick muscle and De Villafranca(5) in developing rat muscle also found a corresponding rise in ATP-ase activity with development of fibrillar substance. As for the organophosphorus compounds (including the corresponding substrate ATP) there are conflicting reports for distribution of acid-soluble phosphorus compounds with age in human(6) and in rat skeletal muscle (7). A recent study by Rockstein, involving both the enzyme system(8) and the related adenine nucleotides(9), important in the energizing of muscular contraction related to flight in insects, revealed a marked decline in the Mg-activated ATP-ase and other enzymes and a concomitant accumulation of

* Supported in part by a grant from U. S. Public Health Service. The authors are appreciative of the early participation and preliminary enzyme determinations, in connection with this study, by Dr. Filomena Boffoli.