STUDIES ON KETONE METABOLISM IN MAN. II. THE EFFECT OF GLUCOSE, INSULIN, CORTISONE AND HYPOGLYCEMIA ON SPLANCHNIC KETONE PRODUCTION [1]

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We have previously described a technique which utilizes hepatic venous catheterization for the estimation of net splanchnic ketone body production (NSKP) in man (1). In a series of subjects without metabolic abnormality, a small but significant endogenous NSKP was detected in the postabsorptive state, and upon the intravenous administration of a ketone body precursor, sodium octanoate, the NSKP was increased fivefold. The present report concerns the application of this technique to the study of the effects of glucose, insulin, cortisone and hypoglycemia on ketone body production in man.

METHODS

Twenty-seven mildly ill male hospital patients between the ages of 23 and 58 years, without metabolic abnormality, were used as subjects and studied after a 12 to 14 hour fast. The criteria of selection and management of subjects, technique of hepatic venous catheterization, methods of chemical analysis, and calculations are identical to those previously reported (1). The 16 normal males in the study will serve as the control series, designated "1955 series," for the present experiments.

The subjects of the present experiments were divided into four groups and studied in a manner similar to the "1955 series" except for the specific metabolic alterations noted below for each group under "Results." The general plan of study for all groups was as follows: After mild phenobarbital sedation, inlying femoral arterial and forearm venous needles and the hepatic venous catheter were inserted. An intravenous infusion of bromsulphalein was started and maintained throughout the period of study. A control study was made on each subject during which femoral arterial and hepatic venous bloods were each sampled four times at five minute intervals for the subsequent determination of bromsulphalein, glucose and total ketone concentrations. A 500 ml. infusion of a 1.5 per cent solution of sodium octanoate was then administered intravenously at a constant rate over a one hour period, during which time blood sampling was repeated four times at 15 minute intervals. Blood sampling for oxygen content and saturation was interspersed at appropriate intervals during each period. The estimated hepatic blood flow (EHBF) was determined by the technique of Bradley, Ingelfinger, Bradley and Curry (2). The net splanchnic glucose production (NSGP) and net splanchnic ketone production (NSKP) are the products of the hepatic blood flow and the hepatic venous-arterial blood glucose and ketone differences, respectively. The net splanchnic oxygen consumption (SPO_2) was calculated by multiplying the arterial-hepatic venous blood oxygen differences by the EHBF.

In addition to the above studies, peripheral venous blood total ketones and glucose concentrations during a four hour insulin tolerance test (0.1 unit per Kg., I.V.) were estimated in 11 normal medical students with and without 200 mg. of cortisone acetate being administered orally one hour prior to the insulin.

RESULTS

1955 series

The data, including the mean plus or minus standard error and standard deviation, for the control series of 16 male subjects previously reported in detail (1), are given at the bottom of Table I. Each subject was studied first in the postabsorptive state, the *control period,* and then during the hour-long infusion of 500 ml. of 1.5 per cent sodium octanoate solution, henceforth designated the *octanoate period.*

Glucose series (Table I)

Six subjects were studied in a manner differing from the 1955 series only in that 20 Gm. of glucose was mixed with the octanoate infusion. Thus, as expected, the data of the control period were entirely comparable to those in the 1955 series of

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TABLE I

The metabolic effects of intravenously administered sodium octanoate mixed with glucose

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Total ketones (μM acetone/100 ml. blood) Control: Fem. art.	Control: Hep. vein	Control: H.V.–F.A.	During sodium octanoate: Fem. art.	During sodium octanoate: Hep. vein	During sodium octanoate: H.V.–F.A.	Δ Fem. art.	Δ Hep. vein	Δ H.V.–F.A.
yrs.											
H. M. 37	Functional G.I. 1.71	1+	22.5	30.3	7.8	58.0	80.0	22.0	+35.5	+49.7	+14.2
W. H. 28	Duodenal ulcer 1.59	1+	11.0	15.8	4.8	45.2	48.2	3.0	+34.2	+32.4	− 1.8
J. F. 31	Duodenal ulcer 1.66	1+	14.5	19.2	4.7	52.5	65.2	12.8	+38.0	+46.0	+ 8.1
H. K. 52	Duodenal ulcer 1.91	1+	13.8	15.8	2.0	34.5	51.5	17.0	+20.7	+35.7	+15.0
T. G. 28	Cervical disc 1.77	1+	9.5	11.8	2.3	27.3	36.8	9.5	+17.8	+25.0	+ 7.2
B. U. 30	Functional G.I. 1.98	1+	10.0	16.0	6.0	25.8	41.5	15.7	+15.8	+25.5	+ 9.7
Mean age, 34 Range, 28–52	Mean S.A., 1.77	Mean S.E. S.D.	13.6 1.97 4.83	18.1 2.81 6.89	4.5 0.87 2.14	40.6 5.46 13.39	53.9 6.57 16.09	13.3 2.68 6.57	+27.0 4.05 9.93	+35.8 4.22 10.34	+ 8.8 2.45 6.00
Statistical comparison with control series		p	>0.5	>0.5	>0.5	>0.5	>0.05 <0.1	<0.01	>0.5	>0.05 <0.1	<0.01
Previously reported control series (16 male subjects)		Mean S.E. S.D.	14.1 1.73 6.92	18.4 2.24 8.96	4.3 0.62 2.46	42.6 2.56 10.25	64.8 2.94 11.79	22.2 1.10 4.40	+28.5 2.26 9.01	+46.4 2.83 11.31	+17.9 1.19 4.77

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Estimated hepatic blood flow ml. blood/min./M.² Control	During sod. oct.	Δ	Net splanchnic ketone production μM acetone/min./M.² Control	During sod. oct.	Δ	Net splanchnic oxygen consumption ml./min./M.² Control	During sod. oct.	Δ
yrs.											
H. M. 37	Functional G.I. 1.71	1+	808	828	+ 20	62	182	+120	34	39	+ 5
W. H. 28	Duodenal ulcer 1.59	1+	548	556	+ 8	28	17	− 11	33	40	+ 7
J. F. 31	Duodenal ulcer 1.66	1+	740	751	+ 11	35	96	+ 61	29	32	+ 3
H. K. 52	Duodenal ulcer 1.91	1+	694	548	−146	16	88	+ 72	28	29	+ 1

TABLE I—*Continued*

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Estimated hepatic blood flow *ml. blood/min./M.²*			Net splanchnic ketone production *μM acetone/min./M.²*			Net splanchnic oxygen consumption *ml./min./M.²*		
			Control	During sod. oct.	Δ	Control	During sod. oct.	Δ	Control	During sod. oct.	Δ
yrs.											
T. G. 28	Cervical disc 1.77	1+	1,106	1,238	+132	28	126	+ 98	36	42	+ 6
B. U. 30	Functional G.I. 1.98	1+	764	819	+ 55	46	129	+ 83	35	46	+11
Mean age, 34	Mean	Mean	777	790	+ 13	35.8	106.3	70.5	32.5	38	+ 5.5
	S.A.,	S.E.	75.3	102.9	34.6	6.60	22.4	18.34	1.35	2.59	1.41
Range, 28–52	1.77	S.D.	184.0	252.1	84.8	16.2	54.8	44.9	3.31	6.36	3.46
Statistical comparison with control series		p	>0.5	>0.3 <0.4	>0.1 <0.2	>0.5	<0.01	>0.01 <0.02	>0.5	>0.4 <0.5	>0.5
Previously reported control series (16 male subjects)		Mean	790	732	− 58.0	34.0	158.0	+124	36.1	40.3	+ 4.2
		S.E.	38.0	40.1	27.15	5.20	6.86	7.36	2.05	1.52	1.46
		S.D.	151.7	160.4	108.6	20.86	27.46	41.4	7.94	5.83	5.66

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Conversion sod. oct. to ketones	Femoral artery glucose *mg./100 ml. blood*			Net splanchnic glucose production *mg./min./M.²*			BSP clearance %		
				Control	During sod. oct.	Δ	Control	During sod. oct.	Δ	Control	During sod. oct.	Δ
yrs.			%									
H. M. 37	Functional G.I. 1.71	1+	14	89	149	+60	50	−30	− 80	94	94	0
W. H. 28	Duodenal ulcer 1.59	1+	0	81	149	+68	62	− 8	− 70	85	83	−2
J. F. 31	Duodenal ulcer 1.66	1+	7	89	140	+51	65	−10	− 75	90	84	−6
H. K. 52	Duodenal ulcer 1.91	1+	10	87	131	+44	72	4	− 68	99	93	−6
T. G. 28	Cervical disc 1.77	1+	12	94	160	+66	96	−41	−137	86	78	−8
B. U. 30	Functional G.I. 1.98	1+	11	81	128	+47	64	−10	− 74	100	103	+3
Mean age, 34	Mean	Mean	9.0	86.6	143	56.4	68.2	−15.8	− 84	92.3	89.2	−3.1
	S.A.,	S.E.	2.02	2.04	4.96	4.12	6.28	6.72	10.73	2.61	3.74	1.73
Range, 28–52	1.77	S.D.	4.96	5.00	12.15	10.1	15.40	16.50	26.30	6.40	9.16	4.23
Statistical comparison with control series		p	<0.01	>0.5	<0.01	<0.01	>0.5	<0.01	<0.01	>0.1 <0.2	>0.2 <0.3	>0.5
Previously reported control series (16 male subjects)		Mean	14.9	84.6	81.6	− 3.0	68.0	65.0	− 3.0	84.4	82.2	−3.4
		S.E.	0.88	1.87	1.76	0.5	4.47	6.0	5.48	3.19	3.32	0.73
		S.D.	3.46	7.46	7.05	2.01	17.92	24.08	21.82	12.81	13.04	2.85

TABLE II

The metabolic effect of intravenously administered sodium octanoate mixed with glucose and insulin

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Total ketones (μM acetone/100 ml. blood) Control: Fem. art.	Control: Hep. vein	Control: H.V.–F.A.	During sodium octanoate: Fem. art.	During sodium octanoate: Hep. vein	During sodium octanoate: H.V.–F.A.	Δ Fem. art.	Δ Hep. vein	Δ H.V.–F.A.
yrs.											
C. M. 39	Cluster headache 1.72	2+	11.0	11.2	0.2	26.7	37.3	10.6	+15.7	+26.1	+10.4
A. H. 28	Duodenal ulcer 1.92	2+	13.5	17.8	4.3	33.0	44.0	11.0	+19.5	+26.2	+ 6.7
A. W. 41	Low back pain 1.76	1+	9.5	12.0	2.5	30.0	48.0	18.0	+20.5	+36.0	+15.5
P. S. 47	Peptic ulcer 1.78	2+	11.0	17.2	6.2	34.0	58.2	24.2	+23.0	+41.0	+18.0
G. F. 33	Epilepsy 1.84	1+	4.2	6.5	2.3	22.0	35.0	13.0	+17.8	+28.5	+10.7
J. G. 30	Peptic ulcer 1.87	1+	12.0	14.7	2.7	31.8	48.5	16.7	+19.8	+33.8	+14.0
C. L. 23	Arrested coccidio-mycosis 1.92	1+	8.8	14.0	5.2	24.5	38.2	13.7	+15.7	+24.2	+ 8.5
E. E. 31	Duodenal ulcer 1.75	1+	36.2	50.8	14.6	52.0	79.5	27.5	+15.8	+28.7	+12.9
Mean age, 34	Mean S.A., 1.82	Mean S.E.	13.3	18.0	4.7	31.8	48.6	16.8	+18.5	+30.6	+12.1
		S.D.	3.41	4.85	1.54	3.25	5.15	2.18	1.04	1.98	1.31
Range, 23–47			9.66	13.72	4.37	9.20	14.58	6.16	2.94	5.61	3.72
Statistical comparison with control series			>0.5	>0.5	>0.5	>0.02 <0.05	<0.01	>0.02 <0.05	<0.01	<0.01	<0.01

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Estimated hepatic blood flow ml. blood/min./M.² Control	During sod. oct.	Δ	Net splanchnic ketone production μM acetone/min./M.² Control	During sod. oct.	Δ	Net splanchnic oxygen consumption ml./min./M.² Control	During sod. oct.	Δ
yrs.											
C. M. 39	Cluster headache 1.72	2+	731	766	+ 35	3	81	+ 78	34	42	+ 8
A. H. 28	Duodenal ulcer 1.92	2+	1,088	1,147	+ 59	46	132	+ 86	31	38	+ 7
A. W. 41	Low back pain 1.76	1+	623	574	− 49	16	100	+ 84	33	33	0
P. S. 47	Peptic ulcer 1.78	2+	820	689	−131	52	167	+115	33	34	+ 1

TABLE II—*Continued*

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Estimated hepatic blood flow *ml. blood/min./M.²* Control	During sod. oct.	Δ	Net splanchnic ketone production *μM acetone/min./M.²* Control	During sod. oct.	Δ	Net splanchnic oxygen consumption *ml./min./M.²* Control	During sod. oct.	Δ
yrs.											
G. F. 33	Epilepsy 1.84	1+	627	632	+ 5	14	82	+ 68	28	38	+10
J. G. 30	Peptic ulcer 1.87	1+	631	633	+ 2	18	106	+ 88	25	34	+ 9
C. L. 23	Arrested coccidio-mycosis 1.92	1+	678	775	+ 97	34	108	+ 74	38	43	+ 5
E. E. 31	Duodenal ulcer 1.75	1+	763	815	+ 52	110	223	+113	37	45	+ 8
Mean age, 34	Mean S.A.,	Mean S.E.	745	754	+ 9	36.6	125.0	+ 88.4	32.4	38.3	+ 5.9
	1.82	S.D.	54.8	63.25	23.70	12.06	17.14	6.07	1.54	1.59	1.31
Range, 23–47			155.0	179.0	67.09	34.12	48.52	17.19	4.36	4.49	3.73
Statistical comparison with control series			>0.5	>0.5	>0.1 <0.2	>0.5	>0.02 <0.05	<0.01	>0.2 <0.3	>0.3 <0.4	>0.4 <0.5

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Conversion sod. oct. to ketones	Femoral artery glucose *mg./100 ml. blood* Control	During sod. oct.	Δ	Net splanchnic glucose production *mg./min./M.²* Control	During sod. oct.	Δ	BSP clearance % Control	During sod. oct.	Δ
yrs.			%									
C. M. 39	Cluster headache 1.72	2+	9	80	106	+26	55	− 7	− 62	79	72	−7
A. H. 28	Duodenal ulcer 1.92	2+	11	86	113	+27	73	+13	− 60	96	91	−5
A. W. 41	Low back pain 1.76	1+	10	82	93	+11	−1	− 2	− 1	70	61	−9
P. S. 47	Peptic ulcer 1.78	2+	14	80	102	+22	58	+ 4	− 54	91	90	−1
G. F. 33	Epilepsy 1.84	1+	8	82	94	+12	91	16	− 75	84	84	0
J. G. 30	Peptic ulcer 1.87	1+	11	82	111	+29	136	+ 2	−134	74	65	−9
C. L. 23	Arrested coccidio-mycosis 1.92	1+	9	79	111	+32	55	0	− 55	79	79	0
E. E. 31	Duodenal ulcer 1.75	1+	13	77	122	+45	56	0	− 56	86	85	−1
Mean age, 34	Mean S.A.,	Mean S.E.	10.7	80.9	106.5	+25.6	65.4	3.4	− 62.0	82.4	78.4	−4.0
	1.82	S.D.	1.88	2.80	9.89	10.95	38.66	7.56	36.38	9.35	11.29	3.96
Range, 23–47												
Statistical comparison with control series			<0.01	>0.1 <0.2	<0.01	<0.01	>0.5	<0.01	<0.01	>0.5	>0.5	>0.5

TABLE III

Total blood ketone and sugar levels during insulin tolerance tests (0.1 unit insulin per Kg. body weight) in 11 normal medical students with and without cortisone pretreatment

		Total blood ketones μM acetone/100 ml. blood						Blood sugar mg./100 ml. blood					
		Fasting	Δ ½ hr.	Δ 1 hr.	Δ 2 hrs.	Δ 3 hrs.	Δ 4 hrs.	Fasting	½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs
Control study	Mean	9.3	−2.4	−2.4	+3.8	+12.9	+16.2	88.0	35.6	67.1	85.4	86.6	85.6
	S.E.	1.38	1.20	1.20	1.72	2.75	3.44	1.66	2.76	3.90	1.90	1.61	1.61
	S.D.	4.47	3.96	3.96	5.50	8.94	11.70	5.51	9.16	12.95	6.30	5.34	5.34
Statistical comparison with fasting levels	p		>0.05 <0.1	>0.05 <0.1	>0.05 <0.1	<0.01	<0.01						
After cortisone	Mean	8.0	−2.4	−0.9	+1.0	+10.7	+12.9	88.7	33.1	70.1	90.4	99.2	99.4
	S.E.	1.38	0.86	1.38	0.86	2.41	3.27	1.46	2.20	4.49	2.44	1.72	1.96
	S.D.	4.30	2.92	4.30	2.75	8.08	11.01	4.84	7.31	14.91	8.12	5.72	6.50
Statistical comparison with fasting level	p		>0.01 <0.02	>0.5	>0.2 <0.3	<0.01	<0.01						
Statistical comparison with control study (p)		>0.5	>0.5	>0.3 <0.4	>0.1 <0.2	>0.5	>0.5	>0.5	>0.4 <0.5	>0.5	>0.1 <0.2	<0.01	<0.01

subjects. After the glucose-octanoate infusion, there was the anticipated elevation of the mean femoral arterial blood glucose level to 143 ± 4.96 (S.E.) mg. per cent and a complete suppression of net splanchnic glucose production. The data on ketone body metabolism in the octanoate period differed from those in the corresponding period in the 1955 series in the following ways: *1*) There was a significant decrease ($p < 0.01$) in the hepatic venous-femoral arterial (HV-FA) blood ketone difference, which was 13.3 ± 2.68 μM per cent compared to 22.2 ± 1.10 μM per cent in the 1955 series; *2*) the mean NSKP was significantly lower ($p < 0.01$) than in the 1955 series, being 106.3 ± 22.4 and 158.0 ± 6.86 μM per minute per M.², respectively; and *3*) the per cent of infused octanoate estimated to be converted to ketone bodies was 9.0 ± 2.02 per cent, a value significantly less ($p < 0.01$) than the 14.9 ± 0.88 per cent found in the 1955 series. In one subject, H.M., the HV–FA blood ketone difference, NSKP and per cent conversion were not significantly different from the 1955 series. In all other subjects the differences were distinct. There were no significant differences in EHBF, SPO_2 or BSP clearance.

Glucose-insulin series (Table II)

Eight subjects were studied before and after the infusion of 20 Gm. of glucose plus 0.1 unit per Kg. body weight HGF-free insulin mixed with sodium octanoate, bringing out only minor differences from the glucose series. Again, the changes were limited to the octanoate infusion period. During the latter, arterial blood glucose levels were lower than those in the glucose series, but NSGP was equally effectively suppressed. Compared to the 1955 series, there were significantly smaller increases in mean arterial and hepatic-venous blood ketone levels and HV–FA blood ketone differences after octanoate infusion in this group ($p < 0.05$, < 0.01 and < 0.05). Similarly, the octanoate infusion induced a smaller net rise in NSKP than in the 1955 series, mean Δ NSKP being + 88.4 ± 6.07 and + 124 ± 7.36 μM per minute per M.², respectively ($p < 0.01$), and the estimated per cent conversion of octanoate to ketone bodies was reduced from 14.9 ± 0.88 per cent to 10.7 ± 0.66 per cent ($p < 0.01$). Although there was no significant difference in the octanoate-period NSKP between this and the glucose series, arterial blood ketone levels were lower in the insulin-glucose group ($p < 0.05$). Indirectly this might suggest that insulin promotes the pe-

ripheral utilization of ketone bodies in the presence of a large carbohydrate load, a concept in distinct contrast to the older observations of Chaikoff and Soskin (3) and Mirsky and Broh-Kahn (4) that neither glucose nor insulin affects the utilization of injected ketone bodies in the eviscerate animal.

While the mean NSKP in this group was significantly lower than that of the 1955 series in the octanoate period, two subjects, P.S. and E.E., attained a net rise in NSKP after octanoate infusion that was comparable to that seen in the 1955 series. In Subject E.E., however, the basal NSKP was approximately three times greater than that in the 1955 subjects. This finding, in the absence of starvation or alkalosis, might reflect the presence of greater anxiety, a potential ketogenic stimulus, than was recognized clinically. In Subject P.S., no explanation is apparent from the data.

Insulin tolerance tests in normal medical students (Table III)

Prior to the hepatic venous catheterization studies reported below in the "Hypoglycemic Series," a pilot study of blood sugar and ketone levels during a standard insulin tolerance test was carried out in 11 normal medical students after an overnight fast.

On the control day, marked hypoglycemia was attained in each subject, with a mean blood sugar level of 35.6 ± 2.76 mg. per cent one-half hour after the insulin. The total peripheral venous blood ketone concentrations showed no significant change from the fasting levels until three and four hours after insulin when there was a net rise of 12.9 ± 2.75 and 16.2 ± 3.44 μM per cent, respectively ($p < 0.01$ for both).[6]

Three days later, the tests were repeated one hour after 200 mg. of cortisone acetate had been administered orally. The degree of hypoglycemia at one-half hour and the rise in venous blood ketone levels during the third and fourth hours were not significantly different from the control day. Blood sugar values three and four hours after insulin (four to five hours after cortisone) rose to significantly higher levels ($p < 0.01$) than did those on the control day. On both the control and cortisone treatment days, there was a tendency for blood ketone concentrations to fall one-half hour after insulin, but this was statistically significant only on the cortisone day ($p < 0.02$). Cortisone pretreatment, in this dosage and timing, did not inhibit the rise in blood ketones during the third and fourth hours after insulin hypoglycemia.

Posthypoglycemic series (Table IV, Figure 1)

Brisk but brief insulin hypoglycemia was induced in six subjects at 7 a.m. by the rapid intravenous injection of 0.1 unit HGF-free insulin per Kg. body weight. Three hours later, at 10 a.m., each was studied in the same manner as the 1955 series before and during the infusion of sodium octanoate. Definite hypoglycemia, approximately 30 minutes in duration, was established in all subjects, the mean lowest blood sugar for the group being 31.0 ± 2.46 (S.E.) mg. per cent.

At the time of study by hepatic venous catheterization, the femoral arterial blood glucose levels and the NSGP had returned to normal control levels, but there were striking changes in ketone metabolism. There were significant increases in the arterial and hepatic venous blood ketone levels and a widening of the HV–FA blood ketone differences, the mean values being 38.8 ± 6.2, 57.6 ± 10.70 and 18.8 ± 5.30 μM per cent, compared to 14.1 ± 1.73, 18.4 ± 2.24 and 4.3 ± 0.62 μM per cent, respectively, in the 1955 series ($p < 0.01$, < 0.01 and < 0.05). Mean control period NSKP was 4.7 times greater than that in the 1955 series of subjects ($p < 0.01$). This is shown graphically in Figure 1. It is interesting to note that mean basal NSKP in the posthypoglycemic subject, 160.7 ± 46 μM per minute per M.^{2}, is almost identical with the mean octanoate period NSKP in the 1955 subjects, 158.0 ± 6.86 μM per minute per M.^{2}. If one could assume that the majority of new ketone bodies produced in the posthypoglycemic state arose from endogenous fatty acids, this might yield a rough estimation of the equivalent quantity of fatty acids being converted to ketones in this state. Despite the elevated basal ketone body levels, this group demonstrated approximately the same increase in blood ketone values

[6] In another group of medical students receiving normal saline I.V., there was a rise in total blood ketones of 5.5 μM per 100 ml. at the end of three hours. This rise was significantly less than that of the hypoglycemic groups ($p < 0.01$).

TABLE IV

Metabolic studies three hours after insulin hypoglycemia

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Total ketones (μM acetone/100 ml. blood) Control Fem. art.	Control Hep. vein	Control Δ	During sodium octanoate Fem. art.	During sodium octanoate Hep. vein	During sodium octanoate Δ	Δ Fem. art.	Δ Hep. vein	Δ H.V.–F.A.
yrs.											
W. C. 42	Duodenal ulcer 1.77	2+	46.0	60.0	14.0	87.5	125.8	38.3	+41.5	+65.8	+24.3
L. G. 58	Duodenal ulcer 1.71	2+	32.0	44.8	12.8	69.0	88.5	19.5	+37.0	+43.7	+ 6.7
G. K. 34	Duodenal ulcer 1.91	1+	45.5	71.5	26.0	80.8	112.5	31.7	+35.3	+41.0	+ 5.7
O. R. 30	Acne vulgaris 1.68	2+	51.8	92.8	41.0	76.5	128.5	52.0	+24.7	+35.7	+11.0
A. B. 33	Functional G.I. 1.99	1+	46.0	61.8	15.8	67.8	98.2	30.4	+21.8	+36.4	+14.6
H. H. 33	Asthma 1.49	1+	11.2	14.8	3.6	42.0	71.0	29.0	+30.8	+56.2	+25.4
Mean age, 38	Mean S.A., 1.76	Mean S.E.	38.8	57.6	18.8	70.6	104.1	33.5	+31.8	+46.5	+14.7
		S.D.	6.12	10.70	5.30	6.40	9.1	4.4	3.08	4.9	3.49
Range, 30–58			15.0	26.30	13.0	15.82	22.4	10.9	7.55	12.0	8.49
Statistical comparison with control series		p	<0.01	<0.01	>0.02 <0.05	<0.01	<0.01	<0.01	>0.4 <0.5	>0.5	>0.1 <0.2

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Estimated hepatic blood flow ml. blood/min./M.² Control	During sod. oct.	Δ	Net splanchnic ketone production μM acetone/min./M.² Control	During sod. oct.	Δ	Net splanchnic oxygen consumption ml./min./M. Control	During sod. oct.	Δ
yrs.											
W. C. 42	Duodenal ulcer 1.77	2+	903	866	−37	126	330	+204	30	32	+2
L. G. 58	Duodenal ulcer 1.71	2+	868	790	−78	111	154	+ 43	36	44	+8
G. K. 34	Duodenal ulcer 1.91	1+	914	826	−88	238	261	+ 23	44	37	−7
O. R. 30	Acne vulgaris 1.68	2+	836	825	−11	345	441	+ 96	43	43	0
A. B. 33	Functional G.I. 1.99	1+	749	801	+52	118	230	+112	36	42	+6
H. H. 33	Asthma 1.49	1+	716	644	−72	26	182	+156	27	28	+1

TABLE IV—*Continued*

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Estimated hepatic blood flow *ml. blood/min./M.²* Control	During sod. oct.	Δ	Net splanchnic ketone production *μM acetone/min./M.²* Control	During sod. oct.	Δ	Net splanchnic oxygen consumption *ml./min./M.²* Control	During sod. oct.	Δ
yrs.											
Mean age, 38	Mean S.A., 1.76	Mean S.E.	831	792	−39	160.7	266.3	+105.6	36	37.7	+1.70
		S.D.	33.4	31.5	21.63	46.0	43.5	27.8	2.70	2.65	2.12
Range, 30–58			81.8	77.1	53.0	112.8	106.5	68.0	6.60	6.50	5.20
Statistical comparison with control series		p	>0.1 <0.2	>0.1 <0.2	>0.5	<0.01	<0.01	>0.5	>0.5	>0.3 <0.4	>0.5

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Conversion sod. oct. to ketones	Femoral artery glucose *mg./100 ml. blood* Control	During sod. oct.	Δ	Net splanchnic glucose production *mg./min./M.²* Control	During sod. oct.	Δ	BSP clearance % Control	During sod. oct.	Δ
yrs.			%									
W. C. 42	Duodenal ulcer 1.77	2+	24	82	74	−8	61	43	−18	80	81	+1
L. G. 58	Duodenal ulcer 1.71	2+	5	85	80	−5	67	47	−20	97	97	0
G. K. 34	Duodenal ulcer 1.91	1+	3	97	91	−6	64	55	− 9	108	108	0
O. R. 30	Acne vulgaris 1.68	2+	11	94	88	−6	119	122	+ 3	90	89	−1
A. B. 33	Functional G.I. 1.99	1+	15	76	75	−1	73	60	−13	79	75	−5
H. H. 33	Asthma 1.49	1+	15	89	81	−8	50	49	− 1	73	70	−3
Mean age, 38	Mean S.A., 1.76	Mean S.E.	12.2	87.1	81.6	−5.5	72.3	62.7	− 9.6	87.8	86.7	−1.1
		S.D.	3.13	3.17	2.75	1.10	9.80	12.1	3.76	5.34	5.82	0.91
Range, 30–58			7.68	7.76	6.74	2.69	24.10	29.7	9.22	13.08	14.25	2.24
Statistical comparison with control series		p	>0.2 <0.3	>0.5	>0.5	0.1	>0.5	>0.5	>0.5	>0.5	>0.4 <0.5	>0.05 <0.1

and NSKP as the 1955 series during the octanoate infusion. In both the control and octanoate periods, mean EHBF, SPO_2 and BSP clearance did not differ significantly from the 1955 subjects.

Cortisone-hypoglycemic series (Table V)

Seven subjects were given 300 mg. cortisone acetate orally at 5 a.m. on the experimental day. Subsequently, they were made hypoglycemic at 7 a.m. and were studied in a manner exactly similar to the "posthypoglycemic series" above. Hypoglycemia was also attained in each of these subjects, the mean lowest blood sugar level for the group being 32.7 ± 2.81 mg. per cent. Due to technical difficulties only a "control period" study was made in Subject D.M.

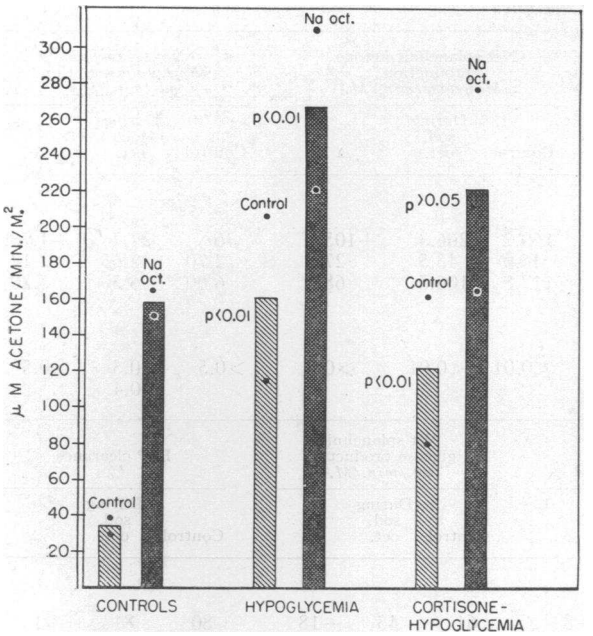

FIG. 1. NET SPLANCHNIC KETONE PRODUCTION BEFORE AND DURING SODIUM OCTANOATE INFUSION IN CONTROL, POSTHYPOGLYCEMIC AND CORTISONE-HYPOGLYCEMIC SERIES OF SUBJECTS (MEAN PLUS OR MINUS STANDARD ERROR)

The p values indicate the statistical comparison between the experimental and control series.

Compared to the posthypoglycemic group, cortisone administered two hours prior to the induction of hypoglycemia did not significantly alter the mean value of any of the measured parameters of carbohydrate or ketone body metabolism. However, closer examination of the ketone data in Table V reveals a remarkable variation of blood ketone levels and NSKP in the individual subjects included in this group. Although comparable degrees of hypoglycemia were attained in each of the seven individuals, Subjects C.P., E.K. and C.F. had the low basal NSKP levels of 37, 41 and 18 μM per minute per M.^{2}, as compared to the mean of 160.7 $\pm$ 46 in the posthypoglycemic group. On the other hand, Subjects E.H. and L.W. varied in the opposite direction with basal NSKP of 299 and 221 μM per minute per M.^{2}. Blood ketone levels revealed a parallel individual variation. Thus, although the mean data in this group indicate that cortisone pretreatment does not affect the ketogenic response to hypoglycemia, the considerable individual variation makes one accept this interpretation with caution.

This group did differ significantly from both the 1955 and posthypoglycemic series in one important respect, the presence of an elevated EHBF in the control period. The mean EHBF in this group was 1,019 $\pm$ 71.92 ml. per minute per M.^{2}, compared with 790 $\pm$ 38 in the 1955 series and 831 $\pm$ 33.4 per minute per M.^{2} in the posthypoglycemic series ($p < 0.01$ and < 0.05). This finding is considered to be a direct or indirect effect of cortisone and is consistent with the previously reported data of Myers and Taylor demonstrating a 43 per cent increase in EHBF following cortisone therapy (5). This effect was partially obscured during the octanoate infusion when there was a fall in EHBF in all three groups.

DISCUSSION

In analyzing the data obtained by this technique it must be kept in mind that we are estimating net *splanchnic* ketone body production. While the viscera and mesentery drained by the portal vein are not the sources of ketone bodies *per se*, the mesenteric adipose tissue unquestionably contributes ketone body precursors as nonesterified fatty acids to the liver. Thus changes in NSKP as herein defined may be determined both by alterations in adipose tissue fatty acid release as well as true hepatic ketogenesis.

The data show that glucose added to an intravenous octanoate infusion significantly reduces the splanchnic ketone production observed when the latter alone is infused in man. The addition of insulin to the glucose-octanoate infusion did not alter the magnitude of this response. This effect of glucose is consistent with the large body of experimental evidence, recently reviewed in detail by Campbell and Best (6), suggesting that carbohydrate exerts its antiketogenic effect by suppressing ketone body production by the liver rather than by influencing peripheral tissue utilization of ketone bodies.

From our data it cannot be determined whether glucose affected the utilization of administered octanoate or simply inhibited endogenous ketone production from fatty acids derived from the liver itself or entering the liver from other sources. Observations by other workers support the conclusion that both mechanisms were influenced to some extent. Dole has clearly shown a sharp decrease

TABLE V

Metabolic studies three hours after insulin hypoglycemia in cortisone pretreated subjects

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Total ketones (μM acetone/100 ml. blood) Control Fem. art.	Control Hep. vein	Control H.V.–F.A.	During sodium octanoate Fem. art.	During sodium octanoate Hep. vein	During sodium octanoate H.V.–F.A.	Δ Fem. art.	Δ Hep. vein	Δ H.V.–F.A.
yrs.											
C. P. 33	Neurosis 1.98	1+	22.2	25.8	3.6	58.5	77.0	18.5	+36.3	+51.2	+14.9
E. K. 29	Neurosis 2.12	1+	12.2	18.2	6.0	23.5	30.8	7.3	+11.3	+12.6	+ 1.3
E. H. 25	Functional G.I. 1.56	1+	67.0	93.0	26.0	122.3	163.3	41.0	+55.3	+70.3	+15.0
W. G. 31	Dermatitis 1.75	1+	49.3	67.0	17.7	94.0	118.2	24.2	+44.7	+51.2	+ 6.5
L. W. 41	Back pain 1.63	1+	52.2	74.0	21.8	93.3	118.3	25.0	+41.1	+44.3	+ 3.2
C. F. 29	Functional G.I. 1.82	2+	12.5	13.2	0.7	38.0	54.8	16.8	+25.5	+41.6	+16.1
D. M. 34	Neurosis 2.00	1+	11.0	18.7	7.7						
Mean age, 32	Mean	Mean	32.3	44.3	12.0	71.6	93.7	22.1	+35.7	+45.2	+ 9.50
	S.A.,	S.E.	8.85	12.58	3.77	15.44	7.73	4.58	6.31	6.26	2.71
Range, 25–41	1.84	S.D.	23.0	37.70	9.8	37.83	18.94	11.22	15.46	15.35	6.63
Statistical comparison with control series		p	<0.01	<0.01	<0.01	<0.01	<0.01	>0.5	>0.1 <0.2	>0.5	<0.01
Statistical comparison with hypoglycemic series		p	>0.5	>0.4 <0.5	>0.2 <0.3	>0.5	>0.4 <0.5	>0.1 <0.2	>0.5	>0.5	>0.2 <0.3

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Estimated hepatic blood flow ml. blood/min./M.² Control	During sod. oct.	Δ	Net splanchnic ketone production μM acetone/min./M.² Control	During sod. oct.	Δ	Net splanchnic oxygen consumption ml./min./M.² Control	During sod. oct.	Δ
yrs.											
C. P. 33	Neurosis 1.98	1+	1,090	1,164	+ 74	37	206	+169	36	41	+5
E. K. 29	Neurosis 2.12	1+	712	670	− 42	41	49	+ 8	42	33	−9
E. H. 25	Functional G.I. 1.56	1+	1,150	1,098	− 52	299	463	+164	34	43	+9
W. G. 31	Dermatitis 1.75	1+	814	687	−127	144	170	+ 26	30	25	−5
L. W. 41	Back pain 1.63	1+	1,015	1,071	+ 56	221	268	+ 47	32	40	+8
C. F. 29	Functional G.I. 1.82	2+	1,202	1,019	−183	18	170	+152	40	43	+3

TABLE V—*Continued*

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Estimated hepatic blood flow *ml. blood/min./M.²*			Net splanchnic ketone production *μM acetone/min./M.²*			Net splanchnic oxygen consumption *ml./min./M.²*		
			Control	During sod. oct.	Δ	Control	During sod. oct.	Δ	Control	During sod. oct.	Δ
yrs.											
D. M. 34	Neurosis 2.00	1+	1,150			88			40		
Mean age, 32	Mean	Mean	1,019	951	− 46	121.1	221.0	+ 94.3	36.3	37.5	+1.83
	S.A., 1.84	S.E.	71.92	88.41	40.85	40.77	56.32	30.61	1.75	2.66	2.71
Range, 25–41		S.D.	187.0	216.6	100.1	106.0	138.0	75.0	4.55	6.51	6.63
Statistical comparison with control series		p	<0.01	<0.01	>0.5	<0.01	>0.05 <0.1	>0.1 <0.2	>0.5	>0.3 <0.4	>0.4 <0.5
Statistical comparison with hypoglycemic series		p	>0.02 <0.05	>0.1 <0.2	>0.5	>0.5	>0.5	>0.5	>0.5	>0.5	>0.5

Patient, Age	Diagnosis, Body surface area	Anxiety during test	Conversion sod. oct. to ketones	Femoral artery glucose *mg./100 ml. blood*			Net splanchnic glucose production *mg./min./M.²*			BSP clearance %		
				Control	During sod. oct.	Δ	Control	During sod. oct.	Δ	Control	During sod. oct.	Δ
yrs.			%									
C. P. 33	Neurosis 1.98	1+	22	102	92	−10	30	76	+46	80	79	−1
E. K. 29	Neurosis 2.12	1+	1	103	96	− 7	154	61	−93	82	75	−7
E. H. 25	Functional G.I. 1.56	1+	17	78	72	− 6	104	52	−52	71	71	0
W. G. 31	Dermatitis 1.75	1+	3	100	87	−13	95	44	−51	60	59	−1
L. W. 41	Back pain 1.63	1+	5	102	96	− 6	66	58	− 8	75	72	−3
C. F. 29	Functional G.I. 1.82	2+	18	97	95	− 2	36	31	− 5	91	86	−5
D. M. 34	Neurosis 2.00	1+		100			121			60		
Mean age, 32	Mean	Mean	11.0	97.4	89.7	− 5.3	86.6	53.6	−27.2	74.1	73.7	−2.8
	S.A., 1.84	S.E.	3.67	3.38	3.47	2.74	17.38	6.28	19.76	4.45	3.68	1.11
Range, 25–41		S.D.	9.0	8.79	8.49	6.71	45.2	15.38	48.4	11.57	9.03	2.72
Statistical comparison with control series		p	>0.1 <0.2	<0.01	>0.02 <0.05	>0.2 <0.3	>0.1 <0.2	>0.2 <0.3	>0.1 <0.2	>0.05 <0.1	>0.1 <0.2	>0.5
Statistical comparison with hypoglycemic series		p	>0.5	>0.05 <0.1	>0.1 <0.2	>0.5	>0.5	>0.5	>0.4 <0.5	>0.05 <0.1	>0.05 <0.1	>0.2 <0.3

in plasma nonesterified fatty acids (NEFA) after glucose or insulin administration in man (7). This has been confirmed by Gordon and Cherkes (8). More recent observations by Gordon suggest that glucose and insulin decrease the liberation of NEFA from depot fat, leading to a decline in blood NEFA levels and finally to a cessation of extraction by other tissues (9). It is of particular interest that in three of his subjects studied by hepatic catheterization, positive arterial-hepatic venous blood NEFA differences were abolished by glucose administration. On the other hand, the *in vitro* studies of Weinhouse, Millington and Friedman (10) and Lossow, Brown and Chaikoff (11) have demonstrated that glucose prefeeding significantly reduced the conversion of labeled fatty acid substrates to both CO_2 and acetoacetate by liver slices. Furthermore, Lossow and Chaikoff (12) have observed that carbohydrate feeding significantly lowered the conversion of C^{14} of several injected fatty acids to CO_2 in intact rats. This effect was far more pronounced in the case of longer-chain fatty acids. However, it should be noted that the longer-chain fatty acids were administered in their experiments as unphysiological, complex emulsions in olive oil, whereas the shorter-chain acids such as octanoate were given as the sodium salt. In similar experiments recently reported by McCalla, Gates and Gordon (13) C^{14} labeled sodium palmitate was administered in the form of a serum albumin-bound complex ion which is believed to be the chemical form of endogenously circulating NEFA. Again, there was a marked inhibition of the conversion of intravenously administered palmitate to CO_2 in the carbohydrate fed intact rat, indicating the occurrence of a block in fatty acid oxidation *per se* at the cellular level. Current evidence suggests that endogenous NEFA are composed almost exclusively of these responsive longer-chain fatty acids (14). Since the carbohydrate sparing of shorter-chain fatty acid (octanoate) oxidation is minimal, we believe that the major carbohydrate effect in our experiments was mediated by a suppression of endogenous fatty acid mobilization or catabolism. In this regard it is noteworthy that the NSKP during the glucose-octanoate infusion experiments was roughly equivalent to the NSKP obtained during the administration of octanoate alone minus the endogenous control period NSKP.

Other data reported herein reveal that hypoglycemia is followed in three to four hours by elevated peripheral venous blood ketone levels, confirming the earlier reports of Collip (15) and Somogyi (16). The basis for this ketonemia in man now seems clearly demonstrated in the hepatic catheterization data in the six subjects which showed a 4.7-fold increase in net splanchnic ketone production three hours after hypoglycemia. This observation lends experimental support to the clinical experience that insulin hypoglycemia may initiate ketosis in the diabetic patient. Since the basal levels of splanchnic ketone production were markedly increased in the posthypoglycemic state, it was at first somewhat surprising to find that octanoate infusion in this group simply induced a net rise in ketone production quantitatively similar to that in the control subjects. This suggests that the ability to utilize the exogenous octanoate for ketone body synthesis is neither augmented nor decreased after hypoglycemia, but rather that the high basal level of ketogenesis is a result either of accelerated utilization of hepatic fatty acids or reflects an increased release of fatty acids from adipose tissue and their delivery to the liver where ketogenesis occurs. Support for the latter concept might be obtained by a study of blood nonesterified fatty acid levels after hypoglycemia, but such data are not recorded in the current literature. The basic biochemical events leading to ketosis in the posthypoglycemic state and their endocrine control have recently been reviewed in detail by one of us (17). The present study throws no light on the endocrine mechanisms involved in the ketonemia consequent to insulin hypoglycemia. However, concurrent studies with rats, to be published elsewhere (18), have shown that this ketosis still occurs in the absence of the pituitary, adrenal cortex and adrenal medulla, and hence hormones from none of these glands are essential. Once ketosis has developed it may be promptly abolished by the administration of a second dose of insulin despite continued hypoglycemia. In fasting hypophysectomized-adrenalectomized rats exhibiting marked hypoglycemia (35 mg. per cent) and ketonemia (258 μM per cent), administration of as little as 0.005 unit of insulin promptly restores blood ketone levels to normal without any further fall in the blood sugar. These data suggest that a relative deficiency in in-

sulin secretion during hypoglycemia may be the single most important hormonal factor contributing to the development of ketosis. It is interesting in this regard that tolbutamide, which reputedly stimulates insulin secretion, is also highly effective in depressing ketonemia during fasting and hypoglycemia (19).

Finally our data show that cortisone pretreatment did not significantly inhibit the elevation in basal net splanchnic ketone production in the posthypoglycemic state. We have pointed out that this interpretation must be accepted cautiously in view of the greater individual variations in this group. However, it is consistent with the recent observation of Amatruda and Engel (18) that cortisone pretreatment does not inhibit the development of ketosis following hypoglycemia in the intact rat. In contrast, it has been shown both in man (20) and the rat (21) that cortisone does inhibit fasting ketosis. Two known metabolic actions of cortisone make it a likely antiketogenic agent in the more slowly developing ketosis of fasting. First, cortisone tends to shift the balance of fat metabolism toward a net accumulation of fat either by inhibiting fat breakdown or stimulating fat synthesis. The second is its action in accelerating carbohydrate production by gluconeogenesis in the liver and in regenerating citric acid cycle precursors from protein catabolism. The answer to the discrepancy in the effect of cortisone on ketosis, suppressing fasting but not modifying posthypoglycemic ketosis, probably resides primarily in the nature of the ketogenic stimulus. It seems likely that the metabolic adjustments rapidly brought forth by the intense stimulus of hypoglycemia outweigh the above-mentioned antiketogenic actions of cortisone, particularly in view of the timing of the present experiments.

An alternate explanation is suggested by the recent finding of Scow, Chernick and Guarco (22) that cortisone is ketogenic in the "totally" pancreatectomized hypophysectomized rat and that this ketosis is prevented by insulin. Cortisone thus may be antiketogenic only when it is capable of bringing about an enhanced rate of insulin secretion. In these terms the variable responses in our cortisone treated posthypoglycemic subjects would reflect variations in the capacity of the pancreas in each case to secrete insulin following suppression by exogenous insulin administration.

SUMMARY

1. Further observations on net splanchnic ketone production (NSKP) were made in metabolically normal human subjects before and after the intravenous infusion of sodium octanoate.

2. The addition of glucose or glucose with insulin to the octanoate infusion significantly lowered the net rise in NSKP noted when octanoate alone was infused.

3. Ketosis in the peripheral blood was observed three hours after the induction of insulin hypoglycemia. While at this time basal NSKP was 4.7-fold greater than in the control subjects, the utilization of infused octanoate was unaffected.

4. Cortisone pretreatment failed to suppress the rise in peripheral blood ketone levels and NSKP occurring in the posthypoglycemic state.

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