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Research Article

THE EFFECT OF EPINEPHRINE, INSULIN, AND HYPERTHYROIDISM ON THE RAPID INTRAVENOUS GLUCOSE TOLERANCE TEST [1]

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Although it is generally accepted that insulin accelerates the removal of glucose from the blood (1, 2), there has been disagreement regarding the effect of epinephrine on glucose utilization in normal individuals (2–5). The effect of hyperthyroidism on glucose tolerance tests has been found to be variable. The present study was undertaken to clarify the effects of epinephrine, insulin, and hyperthyroidism on the rate of removal of glucose from the blood of adult subjects by means of the rapid intravenous glucose tolerance test (6).

MATERIAL AND METHODS

All subjects had been on a diet containing at least 150 grams of carbohydrate daily for at least one week. The rapid intravenous glucose tolerance test was carried out after a 14 hour fast, and the rate of glucose disappearance from the blood was determined as described in a previous publication (6). By this method the range of blood glucose disappearance rates in normal individuals is from 3.00 to 4.84 per cent per minute.

A group of 21 normal males was employed in studying the effect of insulin and of epinephrine. A control test was performed on each subject. The test was performed in 17 of the group, 30 minutes following the subcutaneous administration of 0.5 mg. epinephrine. In a normal individual epinephrine produces a rise in the blood sugar which reaches a maximum within 25 minutes, following which there is a relative plateau for approximately 90 minutes corroborating previous work. In 18 of the group the test was performed immediately after the intravenous administration of 4 units of crystalline insulin. A time interval of approximately one month was allowed to elapse between tests in each subject.

Seventeen patients with uncomplicated hyperthyroidism were studied before treatment with radioactive iodine, and the studies were repeated when a remission of the hyperthyroidism had occurred. All the patients had been on a diet of 5000 calories daily for at least seven days prior to study. A standard oral glucose tolerance test (100 Gm. dose), a basal metabolic rate, and a 24-hour thyroid radioactive iodine uptake were also obtained. The oral glucose tolerance test was interpreted in light of the fasting blood sugar and the blood sugar level at 2 and 3 hours. The macro blood glucose determinations for the oral glucose tolerance test were carried out by the method of Benedict (7).

RESULTS

Epinephrine was found to produce a decrease in the blood glucose disappearance rate (Table I). In the control study, the mean disappearance rate was 3.64, and the range was 3.00 to 4.84 per cent per minute. Following administration of epinephrine, the mean of the disappearance rate was 1.24 and the range 0.83 to 1.82 per cent per minute. The mean of the differences being significant with

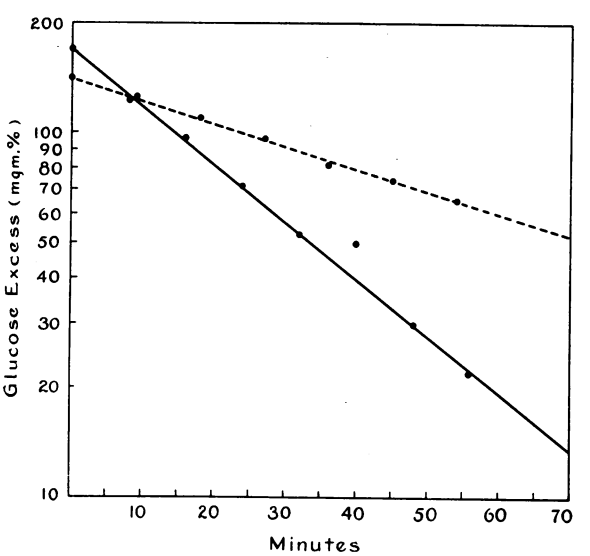

FIG. 1. THE RAPID INTRAVENOUS GLUCOSE TOLERANCE RESPONSE WITH AND WITHOUT EPINEPHRINE IN NORMAL SUBJECT, W. G.

Dotted line is with epinephrine; dark line is the control period.

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P less than 0.01. This change is illustrated in Figure 1.

Insulin produced an increase in the blood glucose disappearance rate. The mean rate in the control study was 3.59, and the range was 3.01 to 4.84 per cent per minute (Table II). After administration of insulin the mean was 7.94 and the range 4.12 to 11.90 per cent per minute. The mean of the differences between the control with and without insulin was significant with P less than 0.01. This change is graphically illustrated in Figure 2.

In moderate to severe hyperthyroidism the disappearance rate of glucose was studied in 17 patients in whom 15 were within the normal or increased range and two were slow. No correlation was found between the glucose disappearance rate and the degree of hyperthyroidism. During the hyperthyroid state, the range of the glucose disappearance rate was 2.42 to 11.17 per cent per minute (Table III). After treatment with radioactive iodine, 15 patients became euthyroid and two patients developed myxedema. Of the 15 patients with disappearance rates of glucose in the normal or increased range prior to therapy, eight became slower, five remained the same and two were slightly increased. The two patients with slow disappearance rates initially became euthyroid after treatment, the disappearance rate returning to normal in one and decreasing in the other. After treatment the range of the glucose disappearance rates was 0.31 to 8.11 per cent per minute with mean of the difference before and after treatment being significant with P less than 0.01. The change in the disappearance rate in patient W. B. is illustrated in Figure 3.

TABLE I—*A comparison of the rapid intravenous glucose tolerance test with and without epinephrine in normal men*

Patient		Fasting glucose	Glucose excess (*mg. %*) 0	8	9	16	18	24	27	32	36	40	45	48	54	56 (*Time in minutes*)	Rate of removal (*%/min.*)
F. R.	a.*	91	215	150		124		114		84		67		57		36	3.35
	b.	111	161		136		134		111		100		88		79		1.12
E. E.	a	110	173	113		80		50		35		25		−3		− 5	4.84
	b.	82	193		192		181		163		151		153		140		0.62
V. K.	a.	102	165	123		103		76		62		45		33		24	3.36
	b.	101	169		158		159		138		130		113		103		0.93
A. B.	a.	97	140	109		85		64		52		39		40		21	3.44
	b.	110	113		98		80		78		75		60		54		1.28
A. Z.	a.	78	196	142		117		90		77		53		46		32	3.30
	b.	150	147		143		132		112		92		70		66		1.36
E. G.	a.	86	175	133		107		94		76		55		45		34	3.01
	b.	140	162		135		128		128		104		93		79		1.23
M. K.	a.	95	170	119		100		82		71		57		38		31	3.01
	b.	105	166		145		143		139		125		113		98		0.86
E. G.	a.	85	187	143		97		63		43		30		−1		−12	4.62
	b.	124	131		125		108		99		84		72		65		1.31
I. P.	a.	84	180	144		112		82		55		28		32		− 3	3.74
	b.	119	161		139		136		135		120		110		103		0.83
W. G.	a.	88	169	123		97		72		53		50		30		22	3.56
	b.	117	140		126		110		96		82		74		65		1.44
W. M.	a.	98	174	133		118		102		74		57		46		34	3.08
	b.	145	144		119		113		105		97		83		67		1.18
W. J.	a.	87	168	130		101		76		58		40		28		13	3.64
	b.	89	130		123		105		101		84		69		66		1.22
W. L.	a.	102	151	108		86		54		56		39		31		24	3.34
	b.	128	104		84		74		62		48		27		35		2.00
N. H.	a.	102	159	118		96		84		72		64		46		34	3.00
	b.	136	134		109		101		94		89		72		59		1.34
G. E.	a.	95	138	99		77		57		43		38		27		21	3.38
	b.	122	100		92		88		83		71		63		59		1.14
F. T.	a.	92	156	114		79		48		37		24		8		−18	4.62
	b.	115	175		162		135		116		110		87		65		1.47
L. S.	a.	92	173	126		86		58		40		28		1		−10	4.62
	b.	123	154		132		110		95		80		68		44		1.82

* a. 25 grams of glucose. b. 0.5 mg. epinephrine given 30 minutes prior to 25 grams of glucose.

TABLE II—*A comparison of the rapid intravenous glucose tolerance test with and without insulin in normal men*

Patient		Fasting glucose	Glucose excess (*mg. %*) 0	8	16	24	32 - 40 (*Time in minutes*)		48	56	64	72	Rate of removal (*%/min.*)
F. R.	a.*	91	215	150	124	114	84	67	57	36	19	19	3.35
	b.	81	185	120	74	36	8	− 9					6.30
E. E.	a.	110	173	113	80	50	35	25	−3	− 5	−15	−18	4.84
	b.	93	177	133	82	48	33	2					5.63
V. K.	a.	102	165	123	103	76	62	45	33	24	11	− 4	3.36
	b.	90	150	105	82	60	42	26					4.12
A. B.	a.	97	140	109	85	64	52	39	40	21	10	1	3.44
	b.	100	116	63	27	13	−21	−27					9.90
A. Z.	a.	78	196	142	117	90	77	53	46	32	15	2	3.30
	b.	97	157	104	49	29	− 7	−25					7.29
E. G.	a.	85	187	143	97	63	43	30	−1	−12	−12	− 7	4.62
	b.	103	185	93	33	−10	−41						9.90
M. K.	a.	95	170	119	100	82	71	57	38	31	26	15	3.01
	b.	96	167	102	55	29	−14	−38					7.37
E. G.	a.	86	175	133	107	94	76	55	45	34	27	12	3.01
	b.	95	173	103	55	30	−22	−32					7.30
I. P.	a.	84	180	144	112	82	55	28	32	− 3	− 9	− 8	3.74
	b.	87	178	107	66	36	21	−17					6.79
W. G.	a.	88	169	123	97	72	53	50	30	22	7	− 5	3.56
	b.	84	148	99	60	42	25	− 2					5.87
W. M.	a.	98	174	133	118	102	74	57	46	34	24	19	3.08
	b.	93	170	92	46	20	−22	−30					8.15
W. J.	a.	87	168	130	101	76	58	40	28	13	8	0	3.64
	b.	100	145	70	31	−26	−46	−40					9.49
W. L.	a.	102	151	108	86	54	56	39	31	24	18	15	3.34
	b.	110	123	66	31	15	0	−13					8.88
R. C.	a.	97	183	141	109	82	65	53	41	26	13	5	3.20
	b.	107	168	114	60	31	8	− 5					7.03
W. H.	a.	98	177	120	92	76	53	41	27	15	3	4	3.84
	b.	96	167	87	39	19	−18	−32					9.24
S. L.	a.	93	137	113	98	72	55	42	37	25	9	9	3.36
	b.	76	182	122	77	38	4	−10					6.30
L. S.	a.	92	173	126	86	58	40	28	1	−10	−10	−14	4.62
	b.	98	144	67	22	−22	−44	−55					11.55
M. P.	a.	98	147	110	87	70	52	41	23	20	14	0	3.30
	b.	96	142	61	21	− 8	−28	−34					11.90

* a. 25 grams of glucose. b. 4 units of regular insulin prior to 25 grams of glucose.

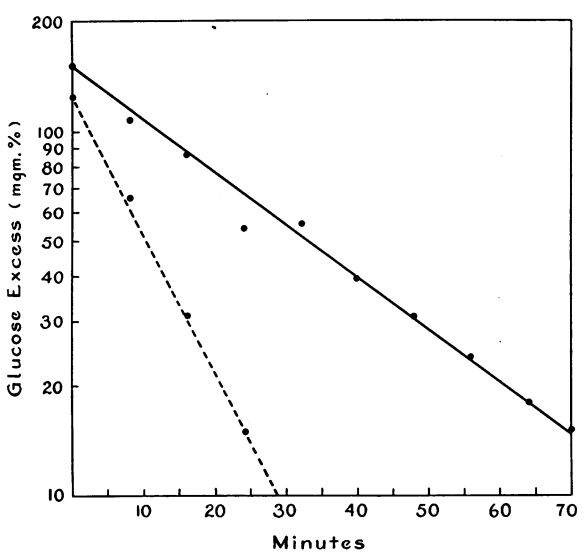

FIG. 2. A COMPARISON OF THE RAPID INTRAVENOUS GLUCOSE RESPONSE WITH AND WITHOUT INSULIN IN NORMAL SUBJECT, W. L.

Dotted line is with insulin; the dark line is during the control period.

In the 16 patients in whom the oral glucose tolerance test was done before treatment, 10 were normal and six were diabetic in type. Of the 10 patients with normal curves before therapy, two became diabetic in type after treatment; of the six patients with diabetic type tests before therapy only four became normal after treatment. No correlation was found between the glucose disappearance rate and the oral glucose tolerance test before or after treatment (Table IV).

DISCUSSION

It has been shown that in normal individuals, maintained on an adequate carbohydrate intake, the rate of disappearance of glucose from the blood during the rapid glucose tolerance test remains constant on repeated tests (6, 8, 9). It is

TABLE III

The rapid glucose tolerance test in the hyperthyroid and euthyroid states

Patient		Fasting glucose	Glucose excess (*mg. %*) 0	8	16	24	32	40	48	56	Rate of removal (*%/min.*)
						(*Time in minutes*)					
W. B.	H.*	113	119	125	72	55	36	25	17	−15	5.08
	E.	85	155	113	95	75	56	39	35	25	3.28
P. E.	H.	113	164	124	89	69	47	40	25	2	3.85
	E.	93	160	117	103	62	46	35	24	1	3.89
C. F.	H.	95	175	132	121	113	85	71	63	45	2.42
	E.	95	195	140	109	75	54	35	27	3	4.20
P. M.	H.	108	150	87	42	18	2	2	2	− 9	8.59
	M.	100	202	150	118	96	82	66	50	38	2.88
M. K.	H.	115	195	141	100	73	44	35	25	−13	4.33
	E.	90	170	136	107	78	47	42	29	12	4.41
J. B.	H.	100	155	125	96	70	62	47	38	24	3.04
	E.	102	180	139	111	88	67	60	48	34	3.04
M. P.	H.	90	168	130	88	66	45	31	10	0	4.47
	M.	95	150	124	98	79	63	48	39	30	3.00
R. R.	H.	88	132	94	65	47	40	24	16	1	4.20
	E.	100	130	100	65	43	29	21	10	5	4.71
W. L.	H.	87	147	117	95	70	59	53	39	28	3.08
	E.	103	144	117	94	78	62	50	39	31	2.86
E. R.	H.	83	164	135	104	87	61	48	37	32	3.30
	E.	110	138	110	85	64	50	34	29	11	3.33
G. G.	H.	88	185	135	101	94	77	55	38	35	3.08
	E.	94	176	124	89	66	43	26	22	6	4.08
H. K.	H.	92	158	118	86	56	38	25	16	5	4.89
	E.	96	184	132	107	77	52	32	28	7	3.74
C. R.	H.	92	156	124	104	85	72	58	48	37	2.66
	E.	107	100	103	97	93	97	93	89	85	0.31
J. F.	H.	101	192	131	94	71	54	34	23	7	4.41
	E.	98	140	120	91	75	64	47	39	32	2.90
R. D. M.	H.	105	130	67	20	−19	−32	−18	−13	− 7	11.17
	E.	115	153	77	34	17	−26	−30	−28	−23	8.11
L. R. S.	H.	98	138	95	72	52	34	22	14	15	4.62
	E.	115	144	105	80	66	46	36	18	12	3.50
S. T.	H.	100	145	85	44	25	4	4	−13	−21	7.57
	E.	77	176	118	69	38	16	13	− 4	−14	6.40

* Clinical status: H. Hyperthyroid, E. Euthyroid, M. Myxedema.

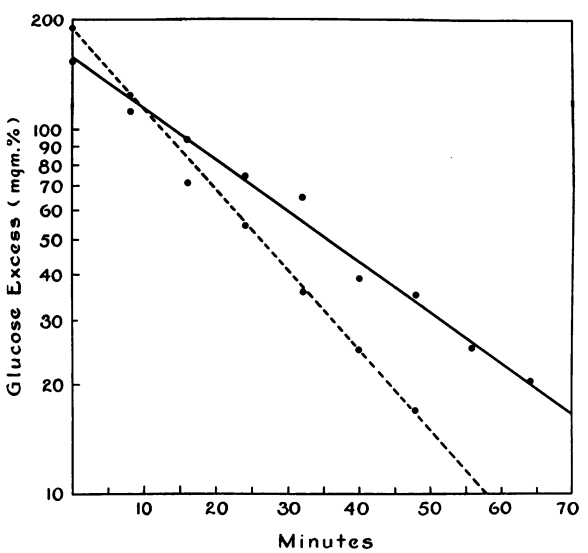

FIG. 3. A COMPARISON OF THE RAPID INTRAVENOUS GLUCOSE RESPONSE DURING THE HYPERTHYROID AND EUTHYROID STATE OF W. B.

Dotted line is during hyperthyroid state; the dark line is at euthyroid state.

known that the administration of epinephrine produces a rise in the blood sugar to a maximum level in about 25 minutes followed by a relative plateau for approximately 90 minutes, probably as a result of hepatic glycogenolysis (10). Epinephrine has also been found to prevent a normal rise in the arteriovenous difference of the blood sugar during the oral glucose tolerance test (2–4). In eviscerated rats, it also has been observed that epinephrine inhibited glucose utilization (11). The present observation of a decreased disappearance rate of glucose by epinephrine in man is probably due to the inability of the liver to assimilate a portion of the excess glucose as glycogen, and in part to a decrease in peripheral tissue utilization of glucose.

The present study is in agreement with previous

work which has demonstrated that insulin accelerates the removal of glucose from the blood (12–14). This increase in the rate of glucose removal may be a reflection of either an increased rate of entry of glucose into the cells (15), or increased phosphorylation of glucose in the hexokinase phase; both mechanisms are probably important.

A diabetic-like response to the oral glucose tolerance test in hyperthyroid subjects has led some observers to postulate an impairment in carbohydrate metabolism. However, direct studies of the action of thyroxine on tissues have revealed that there is an increased uptake of oxygen (16) as well as an increased rate of removal of glucose (17). Other studies have further indicated that the oxidation of glucose is normal or increased in hyperthyroidism (18, 19). The present study revealed that while hyperthyroid, 14 of 16 patients had either a normal or an increased rate of glucose removal from the blood during the rapid intravenous glucose tolerance test. However, five patients with normal or increased glucose disappearance rates had oral glucose tolerance curves which were interpreted as being diabetic in type.

There appeared to be little relationship between the glucose disappearance rates and the oral glucose tolerance curves in the hyperthyroid patients either before or after treatment. It may be that the intravenous glucose tolerance test is a more direct study of the effect of the thyroid hormone on accelerating the *oxidative* processes of all cells. In a similar manner, the diabetic-like curve and the excessive hyperglycemia with the standard oral glucose tolerance test may be due to the effect of the thyroid hormone on accelerating

TABLE IV

The clinical status, the rapid intravenous and oral glucose tolerance tests in the hyperthyroid and euthyroid states

Patient		% Thyroid I-131 uptake	% B.M.R.	Wt. (*lbs.*)	Rate of removal (*%/min.*)	Fasting glucose	Glucose (*mg. %*) (*Time in minutes*) 30	60	120	180
W. B.	H.*	73	+38	138½	5.08	88	204	140	70	77
	E.	48	+ 0	170	3.28	93	202	140	78	68
P. D.	H.	87	+19	167	3.98	89	149	114	114	74
	E.	24	− 3	185	3.89	82	125	90	65	60
C. F.	H.	73	+30	138	2.42	117	150	145	145	103
	E.	30	− 5	141	4.20	77	132	105	77	80
M. P.	H.	71	+35	166	8.59	75	150	135	115	57
	M.	2	−35	193	2.88	85	124	93	90−	83
M. D.	H.	83	−13	130	4.53	86	140	135	94	87
	E.	9	−20	145	4.41	87	139	118	87	73
J. B.	H.	95	+37	138	3.04	76	145	159	137	78
	E.	2	− 8	155	3.04	75	138	108	88	67
P. M.	H.	81	+43	152	4.47	79	155	154	97	75
	M.	3	−26	174	3.00	63	126	158	127	103
R. R.	H.	91	+56	164	4.44	78	180	193	102	71
	E.	42	−15	167	4.71	98	114	84	77	102
W. L.	H.	54	+23	202	3.08	76	172	193	152	100
	E.	39	+ 7	203	2.90	112	215	233	170	108
E. R.	H.	6	+ 9	145	3.30	60	78	189	106	71
	E.	23	+ 4	155	3.33	85	123	148	98	60
G. G.	H.	71	+39	160	3.08	75	158	83	55	68
	E.	13	− 4	165	4.08	85	125	135	110	75
H. K.	H.	73	+42	120	4.89	73	202	224	122	43
	E.	52	+28	122½	3.79	85	215	247	118	56
C. R.	H.	55	+ 2	114	2.66	93	130	103	111	98
	E.	1	−22	118	0.31	94	140	153	130	172
J. F.	H.	88	+35	117	4.41	77	212	224	76	62
	E.	24	+10	145	2.90	80	180	165	79	73
R. D. M.	H.	58	+42	169	11.17	74	137	108	87	72
	E.	23	−12	192	8.11	87	146	133	109	55
L. S.	H.	53	+40	152	4.62	91	177	96	78	82
	E.	1	−20	167	3.50	78	130	107	101	71
S. T.	H.	70	+24	176	7.57	None		None		
	E.	None	+ 7	192	6.40	None		None		

* Clinical status: H. Hyperthyroid, E. Euthyroid, M. Hypothyroid.

the *transferring* mechanisms by the cells of the gastrointestinal tract. Similarly, the flat oral glucose tolerance test in hypothyroidism may indicate a slower *transport* mechanism by the cells of the gastrointestinal tract. This apparent difference may be interpreted as indicating that the rapid intravenous test and the standard oral glucose tolerance test measure different mechanisms of carbohydrate metabolism.

SUMMARY

The disappearance rate of glucose in 17 normal men during the rapid intravenous glucose tolerance test was found to decrease after the administration of epinephrine.

Insulin increased the rate of disappearance of glucose two to three fold in 18 normal men.

In 15 of 17 subjects with hyperthyroidism, the rate of glucose disappearance was found to be normal or increased. After remission of the hyperthyroidism the rate of disappearance of glucose was slower in eight, unchanged in five and slightly more rapid in two patients.

The oral glucose tolerance curves in 6 of 16 patients with hyperthyroidism were interpreted as diabetic in type. Of the six patients who had diabetic-like curves before treatment only four became normal after remission of the hyperthyroidism. Of the 10 patients with normal oral glucose tolerance curves before treatment, two became diabetic-like after therapy.

There was no correlation in the hyperthyroid group between the glucose disappearance rate and the oral glucose tolerance test before or after treatment.

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