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The Effects of Glucocorticoids on Gluconeogenesis in Diabetic and Normal Chinese Hamsters

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THE EFFECTS OF GLUCOCORTICIDS
ON GLUCONEOGENESIS IN DIABETIC AND
NORMAL CHINESE HAMSTERS

by

Charles James Woody

A Thesis
Submitted to the
Faculty of the Graduate College
in partial fulfillment
of the
Degree of Master of Science
Department of Biomedical Sciences

Western Michigan University
Kalamazoo, Michigan
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THE EFFECTS OF GLUCOCORTICOIDS ON GLUCONEOGENESIS
IN DIABETIC AND NORMAL CHINESE HAMSTERS

Charles James Woody, M.S.

Western Michigan University, 1981

The objective of this study was to determine whether diabetic Chinese Hamsters maintained elevated endogenous cortisol concentrations and whether the previously reported elevation in gluconeogenesis in these diabetic animals was correlated with these cortisol concentrations.

It was found that nonketotic diabetic Chinese Hamsters maintained plasma cortisol concentrations similar to those of controls for the morning and evening time periods examined. Their rate of gluconeogenesis and absorption of injected pyruvate is much greater than that of controls in the morning. Furthermore, adrenalectomy increases gluconeogenesis and pyruvate absorption in both diabetics and normals and alleviates the difference seen in these parameters in the intact morning animals. Finally, short term cortisol therapy was unable to restore preadrenalectomy gluconeogenic values in either the diabetic or normal animals.

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Charles James Woody

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INTRODUCTION

The Chinese Hamster (*Cricetulus griseus*) is becoming a widely used animal model for the study of diabetes mellitus in man. Some strains of these animals exhibit spontaneous diabetes, with glucosuria first appearing at four to eight weeks of age and lasting, on an average, of one to eleven months (Chang, Noble & Wyse, 1977). In addition, their diabetes can progress to ketosis (Hunt, Lindsey & Walkley, 1976).

Other strains exhibit a normal fasting blood glucose level of 110 mg%, while nonketotic diabetics average about 250 mg% after a sixteen hour fast (Gerritsen & Dulin, 1967). They differ from human diabetics in that they display a relatively poor response to even large doses of insulin (Gunderson, Yerganian, Lin, Gagnon, Bell, McRae & Onsberg, 1967) and are not obese (Hunt et al., 1976).

Endogenous insulin levels are similar in fasted ketotic diabetics, diabetics, and normals. However, after ingestion of a meal plasma insulin levels rise much higher in the normals than in the diabetics (Gerritsen & Dulin, 1967). From this, and other data, it has been concluded that diabetes in the Chinese Hamster "appears to be caused by a reduced capacity of the pancreatic beta cells to synthesize insulin, beta cell degranulation, glycogen infiltration, and necrosis with a resulting reduction in number of beta cells" (Hunt et al., 1976. p. 1208), as well as the aforementioned reduced responsiveness to exogenous insulin. The etiology of

diabetes in these animals, therefore, is similar to what is believed to occur in humans (Agnew, Aviado, Brody, Burrows, Butler, Combs, Gambill, Glasser, Hine & Shelley, 1965).

Recent literature has established that nonketotic diabetics of several species do not display elevated glucocorticoid levels as was once believed (Exton, 1972; Mortimore, Irvine & Hopper, 1956; Vazquez, Schutt-Aine, Drash & Kenny, 1973). It has been observed, however, that there is a direct correlation ($r=0.96$) between the degree of acidosis in the uncontrolled human juvenile diabetic, and both cortisol secretion rates (CSR) (Sperling, Bacon, Kenny & Drash, 1972) and plasma cortisol concentration (Schadi, Eaton & Standefer, 1978).

The results of many studies support the belief that the elevated CSR found in acidotic diabetics is a result of the "stress" brought on by the diabetic state and is not a function of the diabetes per se (Garces, Kenny, Drash & Preeyasombat, 1969; McArthur, 1954; Sperling, 1977; Sperling et al., 1972). Furthermore, when the acidotic state is corrected there is a return to the normal CSR (Garces et al., 1969; Sperling et al., 1972). It can therefore be stipulated that the "consistent presence of normal CSR in diabetic children without acidosis argues against the contention that the elevated cortisol secretion is a factor in the pathogenesis of juvenile diabetes" (Sperling et al., 1972).

Cortisol secretion rates also appear to be related to acidosis in other species. Elevated adrenocortical function has

been demonstrated in depancreatized dogs only when they are in the acidotic state (Jacobson, 1958). When these diabetic animals were treated for acidosis their glucocorticoid levels did not differ from nondiabetic controls (Jacobson, 1958; Tagnon, 1953).

One anomaly that is widely recognized in the diabetic condition is the increased rates of gluconeogenesis. In vitro studies on alloxan diabetic rats have shown an elevation in the rate of gluconeogenesis in both isolated liver cells and in perfused liver (Exton, 1966; Exton, Harper, Tucker, Flagg & Park, 1973; Shreeve & Hennes, 1958; Wagle & Ingebretsen, 1975). In vivo studies have demonstrated accelerated incorporation of injected labeled gluconeogenic substrate into blood glucose in these diabetic rats (Friedman, 1965; Wagle & Ashmore, 1961). This has also been found to be true for man (DeMuetter & Shreeve, 1963; Friedman, 1965; Wagle & Ashmore, 1961) and hamsters (Chang & Schneider, 1970; Krah1, 1974), both in vivo and in vitro.

Much debate has centered on the cause or causes for this elevated rate of gluconeogenesis in diabetics. Various researchers have established that glucocorticoids are able to accelerate gluconeogenesis both in vivo and in vitro in both normals and diabetics (Briggs & Brotherton, 1970; DeBodo, 1958; Dunn, 1969; Exton, 1966; Exton, 1972; Exton et al., 1973; Fajans, 1961; Froesch, Winegrad, Renold & Thorn, 1958; Haynes, 1962; Krah1, 1974; Landau, Mahler, Ashmore, Elwyn, Hastings & Zottu, 1962; Long, Katzin & Fry, 1940; Munk & Koritz, 1962; Owen & Cahill, 1973; Smith

& Long, 1967; Welt, Stetten, Ingle & Morley, 1952). Their data has shown a decrease in gluconeogenesis following adrenalectomy and restoration of preadrenalectomy gluconeogenic rates with either acute (as little as 30 minutes) or long term glucocorticoid therapy.

Other workers have established that the increased gluconeogenesis found with glucocorticoid treatment is due to the ability of the steroid to increase the supply of gluconeogenic substrates to the liver and is not a direct stimulation of the gluconeogenic pathway per se (Eisenstein, Spencer, Flatness & Brodsky, 1966; Shreeve & Hennes, 1958; Smith & Long, 1967; Wise, Hendler & Felig, 1973). They have found that, in vitro, there is no alteration in the rate of gluconeogenesis following in vivo treatment with varying glucocorticoid concentrations so long as there is an adequate supply of gluconeogenic substrates in the medium.

This appears to be one major variable that further amplifies the elevated gluconeogenesis seen in the diabetic state. It has been demonstrated that the diabetic has an accelerated rate of uptake of gluconeogenic precursors when compared with controls (Chang & Schneider, 1970; Hanson & Mehlman, 1976). Since the criteria for many gluconeogenic studies is incorporation of an injected gluconeogenic precursor, such as pyruvate or alanine, into glucose over a short time interval the diabetic, if better able to utilize the limited amount of substrate introduced in a shorter time, would demonstrate an apparent increased rate of gluconeogenesis.

Additionally, since diabetics have low levels of insulin, it can be reasoned that the diabetic with even normal glucocorticoid levels will have an elevated glucocorticoid/insulin ratio. Because the metabolic effects of glucocorticoids oppose those of insulin (Briggs & Brotherton, 1970) it may be that the elevated gluconeogenesis seen in diabetes is not due to the direct stimulation of the gluconeogenic pathway by glucocorticoids, but to the removal of the inhibition of gluconeogenesis by insulin, and the increased amount of extrahepatic gluconeogenic substrate made available to the liver of the diabetic animal.

It will be the purpose of this paper to establish that both nonketotic diabetic and normal Chinese Hamsters have similar plasma cortisol levels in both the morning and evening and that the elevated gluconeogenic rates previously reported for the diabetic Chinese Hamster (Chang & Schneider, 1970) are not correlated with plasma cortisol levels.

MATERIALS AND METHODS

Animals

All animals used were male Chinese Hamsters from the Upjohn colony. Diabetics (sublines "BD" and "BE") showed a consistent 3+ or 4+ Tes-Tape^(R) value and a negative Ketostix^(R) test. All these animals were matched with control animals (subline "AV") of the same age. The animals were fasted for twenty-four hours prior to the gluconeogenesis studies. At all other times they were allowed food and water ad libitum. The light cycle was regulated for light from 7:00 am to 7:00 pm and the temperature was maintained at about 78° F.

Cortisol Measurement

Plasma cortisol was measured from duplicate 0.05 ml samples utilizing a modification of Murphy's competitive protein-binding radioassay (Murphy, 1967). All bleeding for this and the following assays were done via the orbital sinus. The assay was sensitive enough to detect as little as 0.1 ng of cortisol and had an effective range of about 0 to 400 ng cortisol/ml plasma. A reference plasma sample was included in each assay to assure consistency between assay runs.

Fuller's Earth (30-60 mesh) was utilized as the free cortisol adsorbant. Centrifugation was necessary for the separation of Fuller's Earth from the supernatant. The radioligand reagent was

prepared by adding 0.8 μ C tritiated cortisol to an aqueous solution of 0.8% normal male plasma containing cortisol binding globulin.

Animals were allowed a minimum of four days between bleedings as it was found, in our lab, to be sufficient time for the hematocrit to recover to normal levels after a 0.5 ml blood loss (maximum amount of blood withdrawn from any animal at one time).

Blood Glucose Measurement

Blood glucose levels were determined from 0.1 ml of whole blood using the glucose oxidase method as described in Sigma's Technical Bulletin 510.

In Vivo Gluconeogenesis

Blood 14 C-glucose and blood 14 C-pyruvate levels were measured as described by Chang, 1970. All animals were bled, via the orbital sinus, ten minutes following a 5.0 μ C intraperitoneal (IP) injection of 14 C- pyruvate (New England Nuclear, 3.7 mC/mmol). Conversion to 14 C- glucose was used as the measure of gluconeogenesis (Chang, 1970).

Experimental Procedure

Animals were housed in individual mouse cages upon arrival (day one, see Table I). They were allowed to become acclimated for one week. On day nine, between 9:30 and 10:15 am, 0.5 ml of

blood was removed from each animal. This blood was used for determining morning plasma cortisol concentrations.

On day thirteen, after a twenty-four hour fast, the animals were injected, IP, with 5.0 μ C of ^{14}C -pyruvate. Gluconeogenesis from the injected pyruvate was determined and blood glucose levels were measured. To enable calculation of percent gluconeogenesis from absorbed pyruvate the total amount of ^{14}C present in a 0.01 ml plasma sample was determined and will be referred to as "absorbed pyruvate" (pyruvate present in plasma following the IP injection of ^{14}C -pyruvate).

On day seventeen at 6:00 pm, blood was obtained from each animal in order to measure evening plasma cortisol concentrations. Four days later (day twenty-one) plasma from twenty-four hour fasted animals was assayed for absorbed pyruvate, gluconeogenesis, and blood glucose as before.

On day twenty-five all animals were adrenalectomized using ether anesthesia. Adrenalectomy was confirmed four days later by performing a plasma cortisol assay on each animal. Values below 10 ng/ml were considered indicative of a successful adrenalectomy. Animals were maintained on saline. On the morning of day thirty-three each twenty-four hour fasted animal received an IP injection of either 1.3 mg cortisol dissolved in 0.2 ml sesame oil, or 0.2 ml sesame oil (control). One hour later the animals were injected with 5.0 μ C pyruvate and their plasma assayed for absorbed pyruvate, gluconeogenesis, and blood glucose levels, as before.

This procedure was repeated in the morning on day thirty-seven, substituting the animals receiving cortisol for those that received a sham injection earlier and vice versa. Sufficient blood was taken on this, the last bleeding, to also enable measurement of plasma cortisol concentrations.

Radioactivity measurements were corrected for quenching by the channel-ratio method. The scintillation fluid consisted of 6 g PPO and 50 mg POPOP in 850 ml toluene and 150 ml BBS-3 (Bechman).

The Student's t-test was used in the determination of statistical significance between observed differences. A p value of less than 0.05 was considered significant.

Table I: Experimental procedure outline. See text for explanation.

Day	Procedure
1....	animals placed in individual cages
9....	morning cortisol assay
13....	morning gluconeogenesis assay
17....	evening cortisol assay
21....	evening gluconeogenesis assay
25....	adrenalectomy
29....	cortisol assay on adrenalectomized animals
33....	gluconeogenesis assay on adrenalectomized and adrenalectomized + cortisol treated animals
37....	gluconeogenesis assay on adrenalectomized and adrenalectomized + cortisol treated animals

RESULTS

There was no significant difference in plasma cortisol concentrations between diabetics and normals (Table II). Both displayed low levels in the morning and significant increases in the evening. Percent increases were almost identical for both groups; 76.4% for normals and 77.9% for diabetics.

Table II: Plasma Cortisol Concentrations

Time or Treatment	Cortisol (ng/ml)	
	Normal	Diabetic
am	31.8 \pm 20.3	39.8 \pm 26.1
pm	56.1 \pm 21.3	70.8 \pm 39.8
adrx	0.3 \pm 0.7	2.8 \pm 4.2
adrx + C	1601.0 \pm 470.1	1340.4 \pm 271.3

adrx = adrenalectomized

adrx + C = adrenalectomized + cortisol treatment (1.3 mg)

Each determination is the average of at least seven animals \pm SD

There is no significant difference between diabetics and normals for any time or treatment ($p < 0.05$)

While diabetics did have cortisol concentrations similar to the normals in the morning, all other variables measured differed dramatically. Diabetics had a 93.4% elevation in ^{14}C -pyruvate absorption, a 253.8% increase in gluconeogenesis, a 67.2% increase in percent blood ^{14}C found in glucose, and a 27.3% higher blood glucose level than normals (Table III, Figures 1,2,3). These differences, however, disappeared in the evening. In the evening, normal values for ^{14}C -pyruvate

absorption, gluconeogenesis, and percent blood ^{14}C found in glucose all significantly increased from morning values, whereas diabetic values demonstrated only modest increases. This resulted in normal values for the evening that were statistically equal to evening diabetic values for ^{14}C -pyruvate absorption, gluconeogenesis from injected pyruvate, and percent blood ^{14}C found in glucose. At the same time the difference in blood glucose levels doubled from 27.3% to 55.9% (Table III).

Adrenalectomy produced this same type of pattern. Diabetics are statistically indistinguishable from normals in absorption of pyruvate, gluconeogenesis from injected pyruvate and percent blood ^{14}C found in glucose. Blood glucose levels, however, decreased to a 15% difference, but both diabetics and normals maintained values well below the renal threshold in contrast with preadrenalectomy values for the diabetics.

When these same animals were acutely treated with pharmacological doses of cortisol (in the morning), producing blood cortisol concentrations some 25 to 50 times that of normal, there was virtually no alteration of the responses noted in the adrenalectomized groups (Table III, Figures 1,2,3). The blood glucose levels, however, decreased in the diabetics and increased in the normals so that the two groups have virtually identical blood glucose levels.

When comparing intragroup variations, perhaps the most striking observation concerning the diabetics is that there

Table III: Percent deviation of diabetics from normals at varying times or treatments considering absorption of ^{14}C -pyruvate, gluconeogenesis from injected pyruvate, % blood ^{14}C found in glucose, blood glucose levels, and plasma cortisol levels

% Deviation of Diabetics from Normal Means					
Time or Treatment	Absorption of ^{14}C Pyruvate	Gluconeogenesis from injected Pyruvate	Blood ^{14}C found in Glucose	Blood Glucose Levels	Plasma Cortisol Levels
am	93.4***	253.8****	67.2***	27.3*	25.2 (NS)
pm	-7.9 (NS)	-20.0 (NS)	-16.0 (NS)	55.0*	26.2 (NS)
adrx	30.5 (NS)	57.7 (NS)	25.8 (NS)	15.0**	---
adrx + C	20.0 (NS)	50.7 (NS)	27.6 (NS)	6.6 (NS)	-16.3 (NS)

(NS) = no significant difference from normal values, $p < 0.05$

* $p < 0.05$

** $p < 0.01$

*** $p < 0.005$

**** $p < 0.0005$

adrx = adrenalectomized

adrx + C = adrenalectomized + cortisol treatment (1.3 mg)

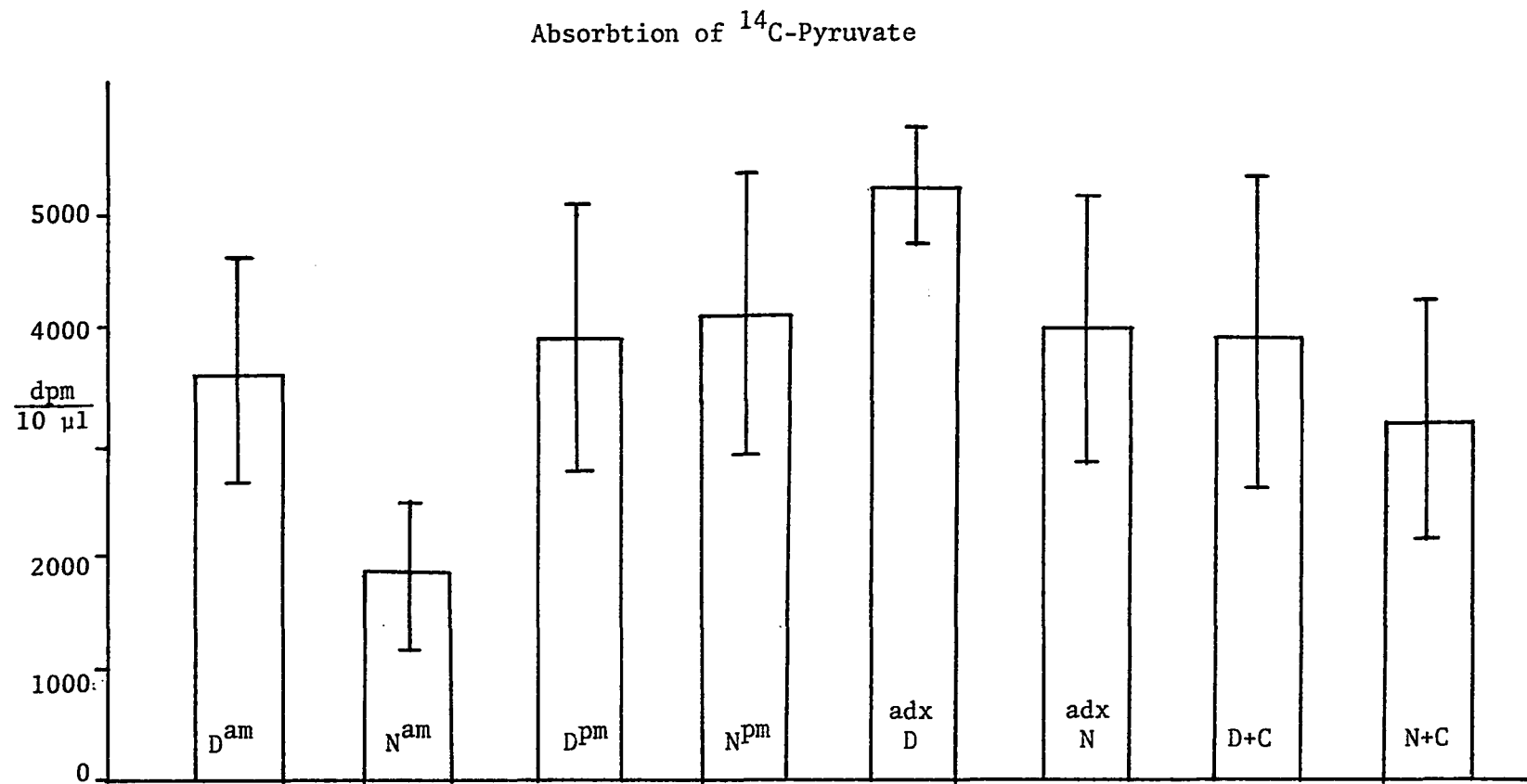


Figure 1: Content of ^{14}C -pyruvate in blood plasma following intraperitoneal injection. Results indicated are average of at least seven determinations \pm SD.

D ^{am} - am diabetic	adx D- adrenalectomized diabetic
N ^{am} - am normal	adx N- adrenalectomized normal
D ^{pm} - pm diabetic	D + C- adrenalectomized diabetic receiving cortisol
N ^{pm} - pm normal	N + C- adrenalectomized normal receiving cortisol

Gluconeogenesis

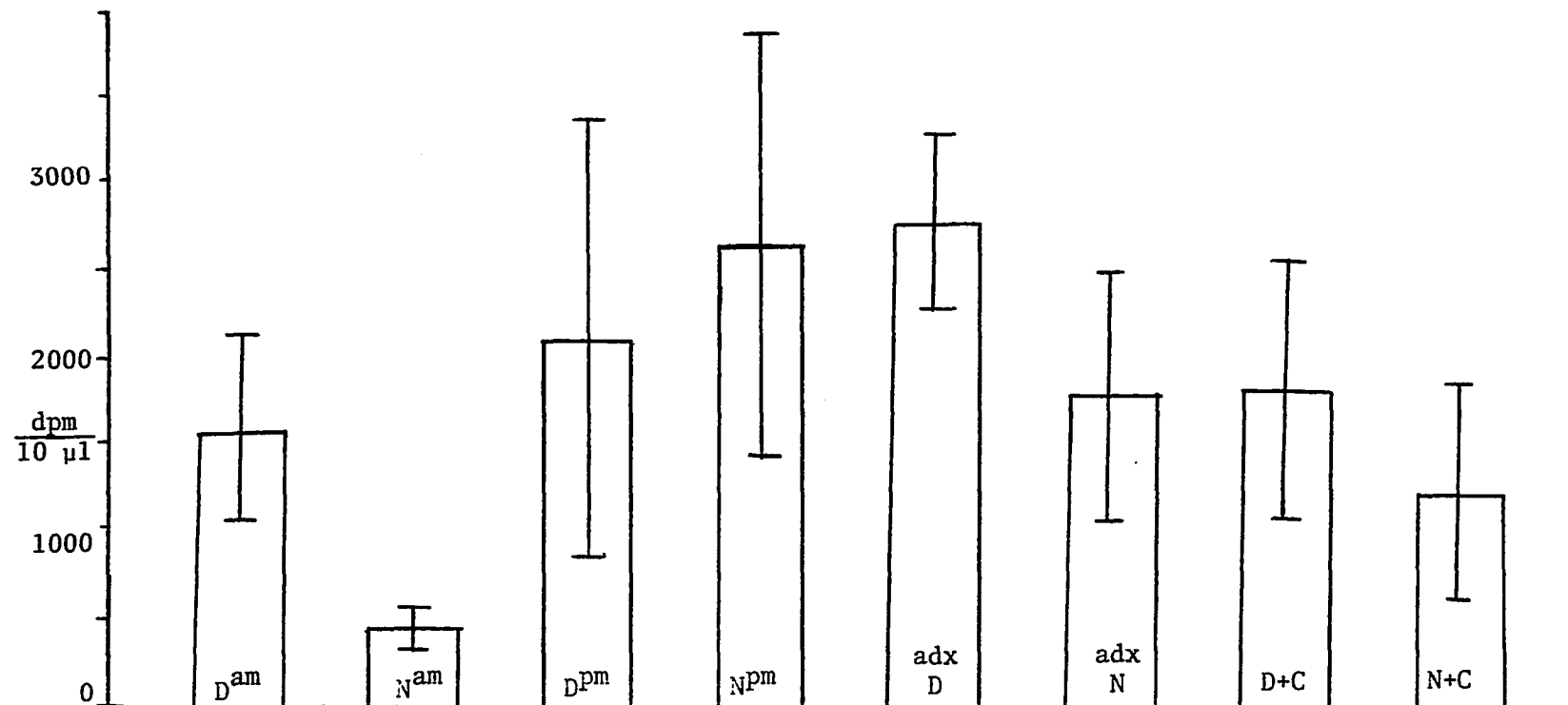


Figure 2: ¹⁴C-Glucose appearing in blood plasma ten minutes after intraperitoneal injection
Results indicated are average of at least seven determinations \pm SD.

D ^{am} - am diabetic	adx D- adrenalectomized diabetic
N ^{am} - am normal	adx N- adrenalectomized normal
D ^{pm} - pm diabetic	D + C- adrenalectomized diabetic receiving cortisol
N ^{pm} - pm normal	N + C- adrenalectomized normal receiving cortisol

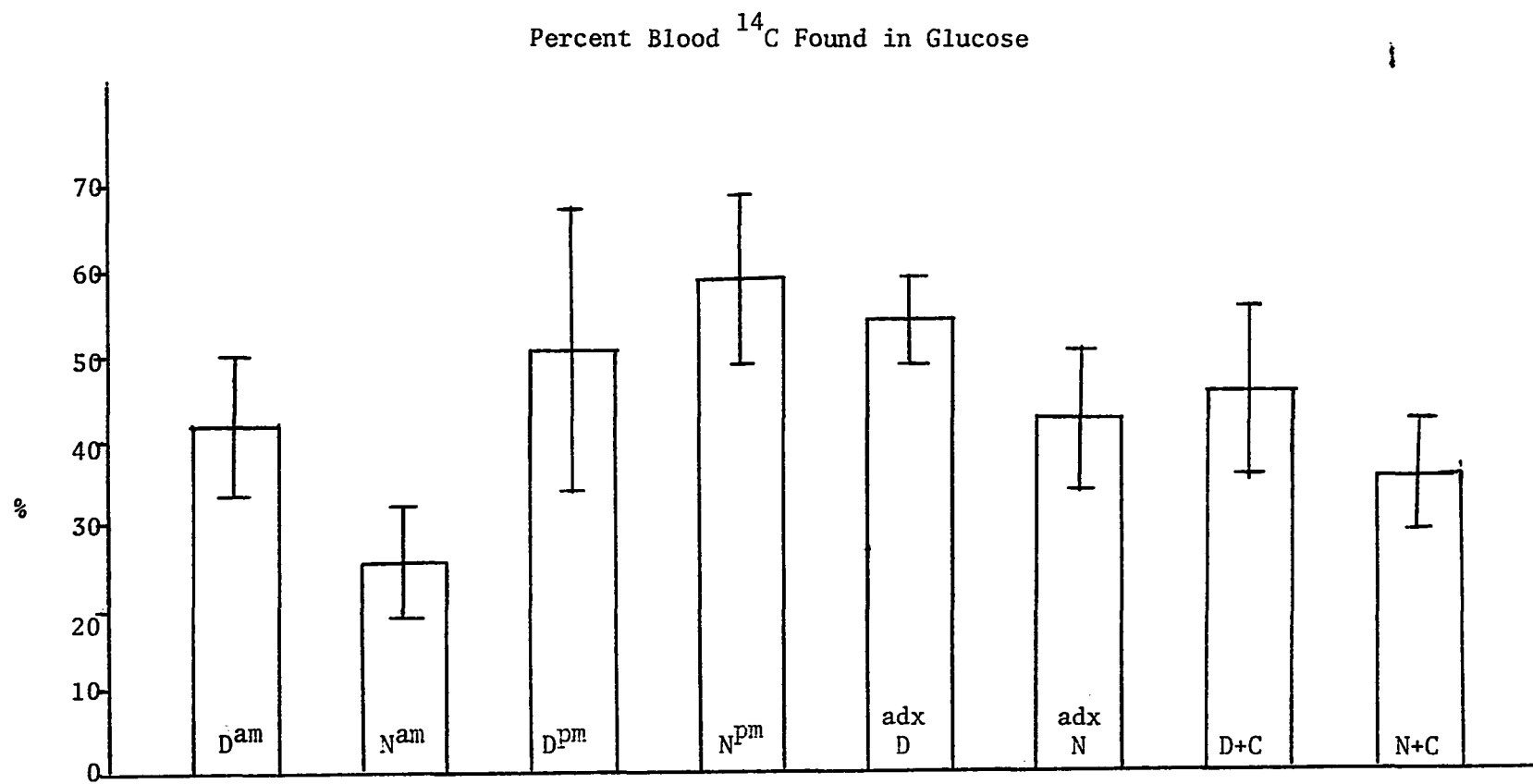


Figure 3: Percent of blood ^{14}C appearing as glucose. Results indicated are average of at least seven determinations \pm SD.

D ^{am} - am diabetic	adx D- adrenalectomized diabetic
N ^{am} - am normal	adx N- adrenalectomized normal
D ^{pm} - pm diabetic	D + C- adrenalectomized diabetic receiving cortisol
N ^{pm} - pm normal	N + C- adrenalectomized normal receiving cortisol

is no significant increase in absorption of pyruvate, gluconeogenesis from injected pyruvate, percent gluconeogenesis, or blood glucose levels between morning and evening values. In the normals these same variables increase by 128%, 490% and 129%, respectively, while the blood glucose remained unchanged (Table III, Figures 1,2,3). This is despite a quantitatively similar increase in cortisol levels (Table II).

Following adrenalectomy, diabetics display a significant increase in pyruvate absorption, gluconeogenesis from injected pyruvate, and percent gluconeogenesis from morning values. They also show a decrease in blood glucose levels to levels below the renal threshold. Normals exhibit a substantially greater increase in pyruvate absorption, gluconeogenesis from injected pyruvate, and percent gluconeogenesis from morning values than do the diabetics following adrenalectomy such that there is no longer any significant difference between the two groups (Table III, Figures 1,2,3). There is also a significant decrease in the blood glucose levels of both the diabetics and normals following adrenalectomy, bringing their values very close to one another; 82.8 mg% for normals and 95.2 mg% for diabetics (Table IV).

Short term cortisol treatment did not restore blood glucose levels to preadrenalectomy values, and resulted in a slight decrease in pyruvate absorption, gluconeogenesis from injected pyruvate, and percent gluconeogenesis, when compared with adrenalectomized values (Table III, Figures 1,2,3).

Table IV: Blood Glucose Levels

Time or Treatment	Blood Glucose (mg%)	
	Normal	Diabetic
am	144.5 \pm 10.9	183.9 \pm 40.0
pm	135.3 \pm 11.4	210.0 \pm 81.2
adrx	82.8 \pm 6.6	95.2 \pm 4.8
adrx + C	86.0 \pm 10.5	91.7 \pm 17.3

adrx = adrenalectomized

adrx + C = adrenalectomized + cortisol treatment (1.3 mg)

Each determination is the average of at least seven
animals \pm SD.

DISCUSSION

Morning values for absorption of injected pyruvate correspond well with those previously reported for the Chinese Hamster by Chang and Schneider (1970b). These data were further supported by work done on human diabetics which has shown a 65-115% increase in uptake of pyruvate in diabetics (Hanson & Mehlmer, 1976), and an overall elevation in uptake of total gluconeogenic precursors (Sestoft, Trap-Jensen, Lyngsoe, Clausen, Holst, Nielsen, Rehfeld & DeMuckadell, 1977).

The elevation of gluconeogenesis by the diabetics (time of day not reported) has been previously reported for the Chinese Hamster both in vivo (Chang & Schneider, 1970b) and for liver slices in vitro (Chang & Schneider, 1970a). Such findings are not unique to the Chinese Hamster and have been reported by a variety of investigators working primarily with alloxan diabetic rats (Exton et al., 1973; Wagle & Ashmore, 1963; Wagle, Ingebretsen & Sampson, 1975).

Morning plasma cortisol levels were statistically indistinguishable in these same nonketotic diabetics as compared with controls, which has also been previously reported to be the case in humans (Garces et al., 1969; Schadi et al., 1978; Sperling et al., 1972) and depancreatized dogs (Jacobson, 1958). It can be concluded from these data that in the morning, after a twenty-four hour fast, diabetic Chinese Hamsters are able to

absorb pyruvate into the bloodstream and maintain gluconeogenesis at a rate greater than normal Chinese Hamsters in spite of equivalent plasma cortisol concentrations. It is therefore apparent that plasma cortisol concentrations do not play a regulatory role in either the absorption of pyruvate or in gluconeogenesis in the morning in the diabetic Chinese Hamster.

Evening values for these same animals represent a somewhat different picture. Both diabetics and normals show similar elevations in cortisol levels characteristic of nocturnal animals, yet only the normals show the concomitant rise in gluconeogenesis. In the evening, pyruvate absorption and gluconeogenesis of the diabetic animals are indistinguishable from the normals or the morning diabetic values. Judging from these data it would appear that the diabetics maintain a constantly elevated rate of gluconeogenesis throughout the day which is close to the maximum levels observed in the normals in the evening.

One possible explanation for this phenomena would be daily fluctuations in key gluconeogenic enzymes for normals, while diabetics maintain a constant, yet elevated level of these same enzymes. Circadian rhythms of gluconeogenic enzymes have been reported in normal and adrenalectomized rats (Wurtman, Shoemaker & Larin, 1968), but none, to the knowledge of this investigator, have been found in diabetic animals. Elevations of phosphoenolpyruvate carboxykinase in the livers of alloxan

diabetic rats have been demonstrated (Lardy, Foster, Young, Shrago & Ray, 1965), but it is not known whether this was characteristic for one time period only or throughout a twenty-four hour cycle.

Following adrenalectomy, morning measurements in both diabetics and normals show an increase in absorption of injected pyruvate, gluconeogenesis from injected pyruvate, and percent blood ^{14}C found in glucose. Previous investigators have produced data that both supports and conflicts with these findings. Dunn and Chenoweth (1969) have demonstrated in vivo a significant decrease in gluconeogenesis from alanine in fasted adrenalectomized rats. Similarly, Exton et al. (1973) demonstrated, in vitro, a decrease in gluconeogenesis from lactate in both alloxan diabetic and normal rat livers following adrenalectomy.

Supporting our findings, Friedmann et al. (1965), found an increase in gluconeogenesis in fasted adrenalectomized and fasted alloxan-diabetic rats as compared with normals, fifteen minutes after injections of ^{14}C -pyruvate. Other researchers have shown, both in vivo and in vitro, similar rates of gluconeogenesis in adrenalectomized and intact rats (Ashmore, Stucker, Lever & Kelsheimer, 1961; Renold, Teng, Nesbett & Hastings; Seitz, Kaiser & Tarnowski, 1976; Steele, Altszuler, Wall, Dunn & DeBodo, 1959).

The decrease in blood glucose levels in both diabetics and normals following adrenalectomy has been reported by several investigators (Dunn & Chenoweth, 1969; Friedmann et al., 1965).

Short term cortisol replacement therapy, while producing dramatic increases in plasma cortisol levels, was not able to

increase the rate of gluconeogenesis in vivo as was reported for the rat in vitro (Exton, 1972; Exton et al., 1973) nor was it able to increase blood glucose levels as was previously reported (Munck & Koritz, 1962). Apparently the effects of cortisol on gluconeogenesis in the Chinese Hamster are minimal, as would be suggested by the lack of correlation between endogenous cortisol levels and rates of gluconeogenesis in the morning and evening time periods studied. Perhaps cortisol requires more time to be effective than has been documented in other species. The lack of an increase in blood glucose levels with cortisol treatment is probably also indicative of the inability of cortisol to significantly increase the rates of gluconeogenesis in these animals.

The increase in gluconeogenesis and pyruvate absorption following adrenalectomy in both diabetics and normals is puzzling. It would appear that gluconeogenesis in these animals is controlled by some system which is circadian in nature in normal animals and giving peak gluconeogenic rates in the evening. In the diabetic, however, this system appears to be relatively constant, maintaining gluconeogenesis at a uniform rate throughout the day, and is inhibited by cortisol or some other product of the adrenal gland. It is obvious that the levels of key gluconeogenic enzymes must be studied in these animals at varying times of the day to answer this question.

In conclusion, our findings indicate that nonketotic diabetic Chinese Hamsters maintain plasma cortisol levels similar

to those of controls for the morning and evening time periods examined. Their rate of gluconeogenesis and absorption of injected pyruvate is much greater than that of controls in the morning, but is not statistically different from controls in the evening. Furthermore, adrenalectomy increases gluconeogenesis and pyruvate absorption in both diabetics and normals and alleviates the difference seen in these parameters in the intact morning animals. Finally, short term cortisol therapy was unable to restore preadrenalectomy values in either the diabetic or normal animals.

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