Journal of Steroid Biochemistry, 1976. Vol. 7, pp. 653–659. Pergamon Press. Printed in Great Britain

ADRENAL–PITUITARY IMPLICATION FOR MAINTENANCE OF TISSUE GLYCOGEN STORES IN CYCLIC AND PREGNANT RATS

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(*Received* 9 *February* 1976)

SUMMARY

The influence of adrenal steroidogenesis upon glycogen storage during pregnancy and oestrous cycle in rats was studied. Adrenal steroids were totally supressed or inactivated by adrenalectomy or hypophysectomy of the cyclic as well as pregnant animals. The variations in glycogen reserves of heart, uterus and liver which take place during normal pregnancy were recorded from day 14 post-coitum to 24 h post-parturition. Uterine glycogen increased markedly from day 18 to the time of delivery. On the other hand hepatic glycogen decreased during 18 and 21 days of gestation. The effects of adrenalectomy and hypophysectomy during pro-oestrous phase of the oestrous cycle were qualitatively different from those of pregnant animals. Both surgical ablations increase uterine glycogen in pregnant females but similar treatment to rats in pro-oestrous phase of the cycle declined glycogen content of the uterus. The administration of compensatory doses of cortisol to adrenalectomized females or ACTH to hypophysectomized animals produced important alterations in glycogen stores of all the three organs studied. Cortisol administration to adrenalectomized females in pro-oestrous phase greatly increased uterine and cardiac glycogen whereas similar treatment to pregnant adrenalectomized rats showed marked increase only in the heart. ACTH treatment increased hepatic and cardiac glycogen in rats hypophysectomized during the cycle but the pregnant females subjected to ACTH administration showed increase only in the heart but liver glycogen declined. The compensatory treatment of adrenal and pituitary hormones to pregnant and cyclic animals provides evidence in support of the hypothesis that these hormones have an important role for the regulation of carbohydrate metabolism in heart, uterus and liver not only during normal life but also during pregnancy and oestrous cycle.

INTRODUCTION

Carbohydrate metabolism in non-pregnant and pregnant animals has been a subject of extensive investigation by several authors [1–5]. All these latter studies have been concerned with cyclic changes in glycogen concentration of the uterus. There is little information available about glycogen regulation in organs other than uterus and the biochemical events during pregnancy and oestrous cycle [3, 6]. The highest content of glycogen in the non-pregnant rat's uterus is found at pro-oestrous [1]. Recently the influence of repeated injections of oestradiol and progesterone on uterine glycogen at different phases of the oestrous cycle has been reported [6, 7]. The investigations during pregnancy have been mainly elaborated from 0 to 12 days post-coitum and little is known regarding the biochemical actions of endocrine secretions on glycogen storage during late pregnancy. Progressive increases in uterine stocks of glycogen between 2–7 days of pregnancy were observed long back [8]. The activities of phosphofructokinase, glucose-6-phosphatase and 6-phosphogluconate dehydrogenase in the uterus vary from the start of gestation [9]. Recently it was again shown that uterine glycogen increases progressively during 0 to 4 days of gestation but these increases were followed by a decrease between 4–6 days post-coitum [10]. The increases in glycogen on day 4 of gestation have been related to increased oestrogens and decreased progesterone levels at the same interval [11–13]. This hypothesis has been opposed by Greenstreet and Fotherby [6] who elaborately analysed many intermediate parameters and enzymes of glucose metabolism. They interpretated the variations in glycogen content of the uterus as a consequence of blastocyte implantation.

The present study was undertaken to investigate glycogen storage in the rat uterus, heart and liver from day 14 of gestation to 24 h post-parturition. Since glycogen homeostasis represents a complex interaction between several hormones, the influence of adrenalectomy and hypophysectomy on glycogen reserves during pregnancy and pro-oestrous phase of the oestrous cycle was determined. The animals deprived of their adrenals and pituitaries were also given compensatory doses of cortisol or ACTH to find the specific action of these hormones upon glycogen storage.

MATERIALS AND METHODS

Albino female rats of Sherman strain obtained from Janvier, Paris, were used in all experiments. The females weighed 250 ± 50 g and were housed at a constant temperature of 21°C ± 1°C with natural day and night cycles during May–December. The different

phases of the oestrous cycle were determined by microscopic examination of vaginal smears. The animals were fed with commercial laboratory food *ad libitum*. The females were impregnated by keeping one male in the cage of seven females only once from 6 p.m. to 9 a.m. The fertilization was supposed to occur at 2 a.m. Thus it was possible to estimate the day of pregnancy ± 7 h. The females were isolated in individual cages and palpated 14 days later for verification of pregnancy. If so, at 2 p.m., they were considered to be pregnant for $14\frac{1}{2}$ days. Under normal conditions parturition occurred during days $21\frac{1}{2}$ to 22 of pregnancy [14].

All the endocrine ablations were performed on day 15 of pregnancy or during well defined pro-oestrous phase of the oestrous cycle. All the operations were made under ether anaesthesia. Adrenalectomy was performed bilaterally and the operated animals were maintained on 0.9% saline. Hypophysectomy was made parapharyngeally [15]. No important modification in time of parturition was observed with the two operations since all the animals were sacrificed on 21 day post-coitum. The operated animals were verified for validity of the operations since identification data about each animal was recorded.

Hormone administrations. The administration of different hormones was started the day after the operation and it lasted for five days. Hydrocortisol (3 mg/100 g body weight for 5 days) and ACTH (1.3 IU/100 g body weight for 5 days) were administered subcutaneously every day at 10 a.m. On day 6, the animals were killed by neck fracture and the tissues were excised immediately and placed on a watch glass at 0°C. Livers, hearts and uteri obtained were analysed immediately for glycogen content. All the tissues were blotted dry before conversion to assay tubes containing 60% KOH.

Assay of glycogen. Glycogen was extracted according to the principle of Slosse [16] by dissolving the tissues in 60% KOH and its further conversion to glucose. For each assay, about 1 g of liver, heart or uterus was taken, cut into small pieces and transferred to a screw cap assay tube containing 1 ml of 60% KOH. The tubes were incubated in a water bath at 100°C for 3 h. At the end of incubation, 4 ml of twice distilled water was added to each sample and the tubes were cooled. To accelerate precipitation, 0.5 ml of 20% sodium acetate and 10 ml of 95° ethyl alcohol were added to each tube. The tubes were placed in a freezer at −30°C for at least 1 h as the excessive time did not interfere with the process of precipitation. At the end of precipitation, the tubes were shaken mechanically for 10 min, centrifuged at 3000 rev./min for 5 min and the supernatant was discarded. The precipitate was washed three times with 60% ethyl alcohol and finally with 10 ml of 95° ethyl alcohol. The precipitate was dried in a water bath at 100°C. When dry, 10 ml of boiling distilled water and 0.67 ml of concentrated HCl (d: 1.175) were added. The tubes were sealed firmly and incubated for 1 h at 100°C for conversion of glycogen to glucose. After incubation, the contents of the tubes were neutralized with 60% KOH and pH was adjusted to 7 with the help of glass electrode. The vol. of each tube was adjusted to 15 ml and the contents were assayed for glucose by the method glucose oxidase [17]. The details of the calculations and experimental conditions have been given elsewhere [18].

Statistical differences were calculated using Fisher's Student *t* test. The mean values have been expressed with standard errors.

RESULTS

Tissue glycogen stores during pregnancy. In these studies the glycogen contents (mg/g tissue) of pro-oestrous phase of oestrous cycle were taken as control values. The glycogen reserves are markedly higher during pregnancy than in the pro-oestrous phase (Fig. 1). During the course of gestation, we observed an increase in glycogen stores of uterus during 14 and 17 days post-coitum following by a second increase between day 21 post-coitum and delivery. After reaching the maximum value at 0 h parturition, glycogen stores of uterus declined rapidly at 24 h post-parturition (46% of the value of 0 h parturition). At 24 h post-parturition, uterine glycogen is not significantly different from that of pro-oestrous females.

The livers of pregnant females contain less glycogen than the livers of normal females in pro-oestrous

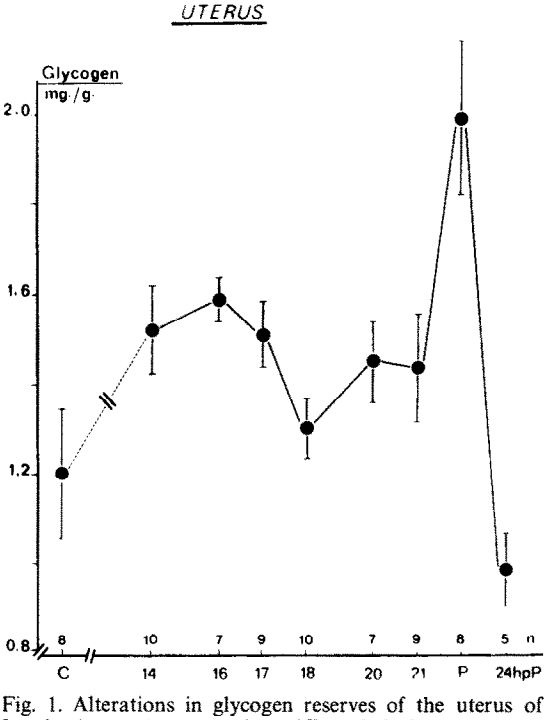

Fig. 1. Alterations in glycogen reserves of the uterus of females in pro-oestrous phase (C) and during pregnancy (14, 16–18, 20, 21 days post-coitum); P (parturition); 24hpP (24 h after delivery). n = number of animals used for each group. Significance of differences between points: C vs day 16, $P < 0.001$; P vs day 18, $P < 0.001$; P vs day 24hpP, $P < 0.001$; C vs day 24hpP, Not Significant.

phase. The decrease to the minimum level can be seen on days 17 and 21 of pregnancy where the stocks of glycogen represent nearly 50% of the pro-oestrous value (Fig. 2). At 18 days post-coitum there was a marked and significant increase from the value of 17 days post-coitum but despite this increase the mean value at 18th day of pregnancy still remained 27% lower than the pro-oestrous value. After a decline upto the 21st day of pregnancy, hepatic glycogen stocks continued to decline after the parturition.

Figure 3. Compared to respective pro-oestrous values, the cardiac glycogen reserves are decreased to a lesser degree during 14 to 20 days of pregnancy than hepatic glycogen in pregnant females during similar intervals. The value at 17 days post-coitum is 30% lower than the pro-oestrous value. As in the liver, there was an increase in stores of heart glycogen from 17 day post-coitum to day 20, following which it rapidly fell to its lowest value at parturition. The observed increases in glycogen on day 20 of pregnancy were not statistically different from control

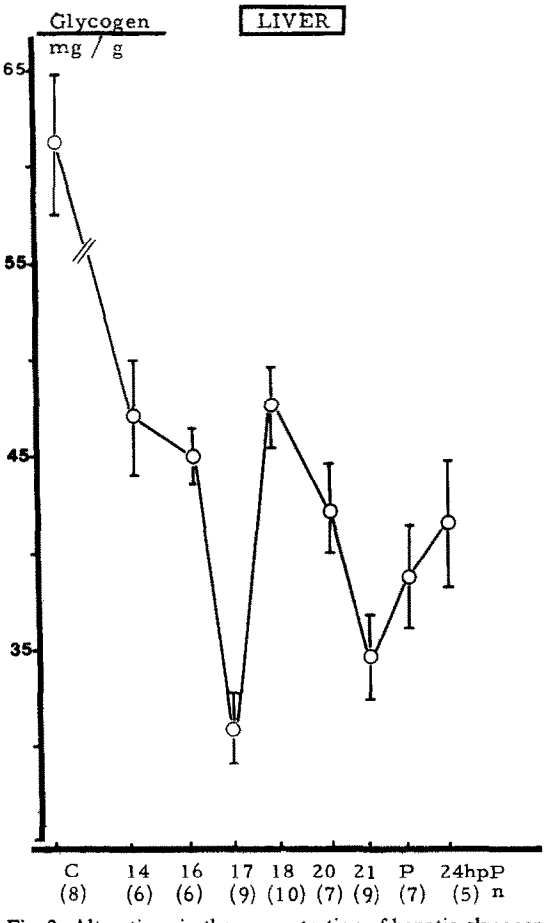

Fig. 2. Alterations in the concentration of hepatic glycogen in rats during pregnancy. C = rats in pro-oestrous phase; 14, 16–18, 20, 21 = days of pregnancy; P and 24hpP = 0 and 24 h after parturition; n = number of animals used. Significance of differences between the points; C vs days 16 & 17, $P < 0.001$; C vs day 18, $P < 0.02$; day 17 vs day 18, $P < 0.001$; day 20 vs day 21, $P < 0.05$; day 18 vs day 21, $P < 0.001$.

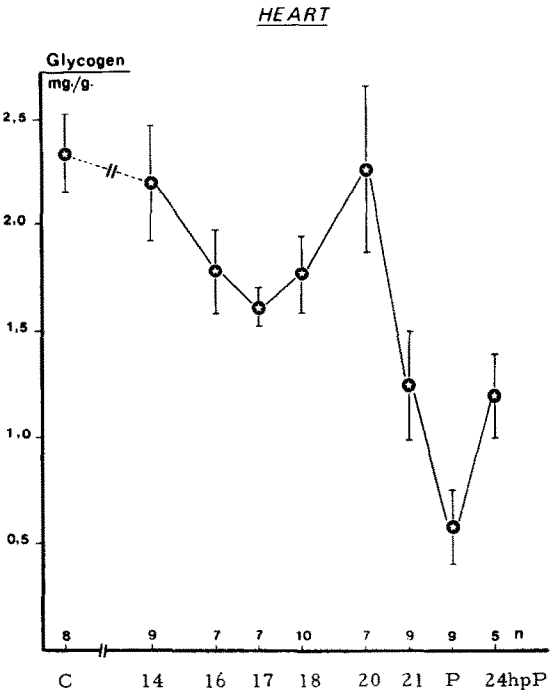

Fig. 3. The glycogen content of rat heart during last part of pregnancy, parturition and post-parturition. C = pro-oestrous value; 14 to 21 = days of gestation; P and 24hpP = 0 and 24 h post-parturition; n = number of females used. Significance of differences between points; C vs day 17, $P < 0.005$; C vs day 21, $P < 0.02$; C vs P, $P < 0.005$; P vs 24hpP, $P < 0.05$; day 20 vs P, $P < 0.001$.

value. At parturition, glycogen store in the heart was at its lowest (75% lower than pro-oestrous heart). Twenty-four hours after parturition an increased accumulation of glycogen in the heart can be seen, which is 100% higher than the value at parturition.

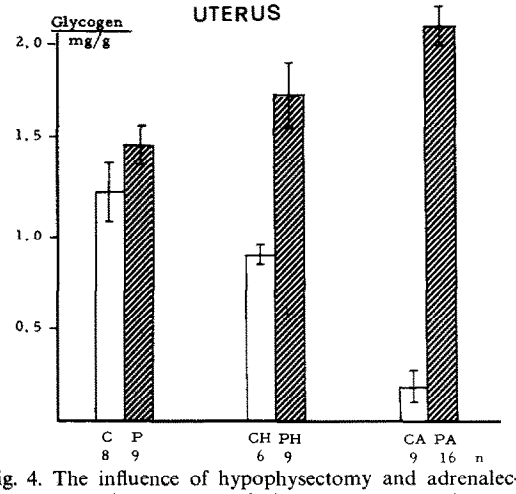

Fig. 4. The influence of hypophysectomy and adrenalectomy on uterine glycogen during pro-oestrous phase of the oestrous cycle and 15th day of pregnancy. C = pro-oestrous value; P = pregnant value at 21 days post coitum; CH and PH = cyclic and pregnant females hypophysectomized; CA and PA = cyclic and pregnant females adrenalectomized; n = number of animals used for each group. The animals were killed 6 days after the operations. Significance of differences between the experiments: C vs CA, $P < 0.001$; C vs CH, $P < 0.05$; 21d vs PA, $P < 0.001$.

The influence of hypophysectomy and adrenalectomy on tissue glycogen storage in normal and pregnant rats. The two surgical ablations of the endocrine glands in females of pro-oestrous phase resulted in a decline of glycogen reserves of uterus. The glycogen contents of the uterus after hypophysectomy and adrenalectomy declined by 29% and 84% when compared to non-operated pro-oestrous values (Fig. 4). The effects of the two surgical ablations in pregnant rats were completely different since marked increases in glycogen reserves of uterus were observed (20% after hypophysectomy and 44% after adrenalectomy).

Figure 5 illustrates the modifications in glycogen reserves of the heart of pregnant and pro-oestrous rats subjected to hypophysectomy and adrenalectomy. These alterations in cardiac glycogen were comparable with that of the uterus, except that the effects of the two hormonal ablations were more severe in this organ. Hypophysectomy declined glycogen stores of heart during pregnancy as well as during pro-oestrous phase by 20% and 75% of their respective control values. This change in pregnant animals was not statistically different from its control value. Adrenalectomy did not affect glycogen storage of the heart of pregnant females but in pro-oestrous phase a 80% reduction was seen which is significantly different from control value.

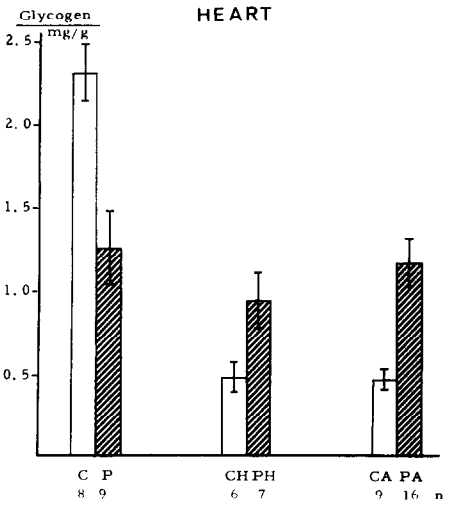

Fig. 5. Variations in stocks of glycogen of heart of cyclic females (C) and pregnant females (P) after adrenalectomy (CA for cyclic) and (PA for pregnant); hypophysectomy (CH for cyclic and PH for pregnant). The cyclic females were operated during pro-oestrous phase of the oestrous cycle. The pregnant females were operated on 15th day of pregnancy. All the females were killed 6 days later. n = number of animals used. Significance of differences between groups: C vs CH, $P < 0.001$; C vs CA, $P < 0.001$. Hypophysectomy did not produce any significant effect in pregnant rats.

Table 1. The effect of adrenalectomy and compensatory treatment with hydrocortisone on glycogen stores

Treatment		Uterus	Heart	Liver
Pro-oestrous (C)	absolute value	1.2 ± 0.12 (8)*	2.34 ± 0.19 (8)	58.0 ± 3.9 (8)
Pregnant 21 days (P)	absolute value	1.44 ± 0.14 (9)	1.24 ± 0.24 (9)	34.7 ± 2.2 (9)
Adrenalectomized in	absolute value	0.19 ± 0.08 (10)	0.48 ± 0.06 (10)	62.4 ± 4.3 (9)
Pro-oestrous (CA)	% of pro-oest.	16	21	108
Adrenalectomized during pregnancy (15 days) (PA)	absolute value	2.07 ± 0.1 (16)	1.19 ± 0.15 (16)	37.6 ± 5.9 (11)
	% of 21d preg.	144	96	108
CA + Hydrocortisone**	absolute value	0.35 ± 0.03 (6)	3.5 ± 0.4 (6)	41.6 ± 1.1 (6)
	% of operated	184	729	66
	% of pro-oest.	29	150	69
PA + Hydrocortisone**	absolute value	2.6 ± 0.19 (12)	1.98 ± 0.2 (12)	44.7 ± 2.9 (12)
	% of operated	126	166	118
	% of 21d preg.	180	160	129

Significance of difference between different groups:

		Uterus	
CA	Vs	CA + Hydrocortisone	No Significance
C	Vs	CA + Hydrocortisone	$P < 0.001$
PA	Vs	PA + Hydrocortisone	$P < 0.02$
P	Vs	PA + Hydrocortisone	$P < 0.001$
		Heart	
CA	Vs	CA + Hydrocortisone	$P < 0.001$
C	Vs	CA + Hydrocortisone	No Significance
PA	Vs	PA + Hydrocortisone	$P < 0.005$
P	Vs	PA + Hydrocortisone	$P < 0.05$
		Liver	
CA	Vs	CA + Hydrocortisone	$P < 0.001$
C	Vs	CA + Hydrocortisone	$P < 0.005$
PA	Vs	PA + Hydrocortisone	No Significance
P	Vs	PA + Hydrocortisone	$P < 0.02$

Values in parenthesis represent the number of animals.

* mg glycogen/g of wet weight.

** The animals were injected for 5 days with 3 mg of hydrocortisone/100 g body weight.

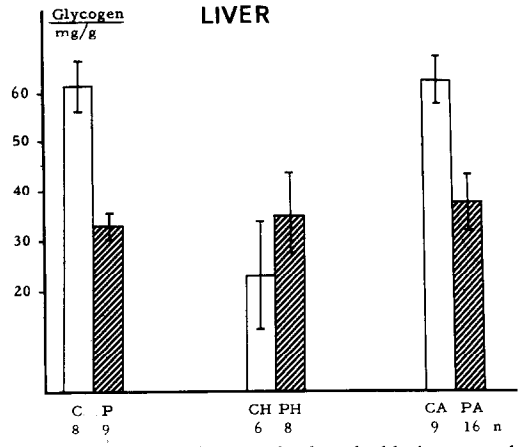

Fig. 6. Effects of pituitary and adrenal ablations on glycogen reserves of livers of rats during pro-oestrous phase (C) and at day 15 of pregnancy (P). CH, CA = females hypophysectomized and adrenalectomized during pro-oestrous phase of the oestrous cycle; PH and PA = females hypophysectomized and adrenalectomized on day 15 of post-coitum. All the animals were killed 6 days after the operations. Significance of differences between groups: C vs CH, $P < 0.005$.

The alterations in glycogen content of liver after hypophysectomy and adrenalectomy of pregnant and pro-oestrous females are shown in Fig. 6. Hypophysectomy of the females in pro-oestrous phase was followed by decline in glycogen content. The pregnant females were not affected by hypophysectomy. Adrenalectomy of the pregnant as well as cyclic females did not show any change of statistical significance from the respective control values.

The effects of exogenous administration of hormones on glycogen. The effects of adrenal and pituitary hormones for the regulation of glycogen stores in the uterus, heart and liver are analyzed in Tables 1 and 2. The results provide a comparison between pro-oestrous and pregnant females for the effects of cortisol and ACTH administration respectively to adrenalectomized and hypophysectomized rats. The absolute values as well as % of the operated and non-operated controls have been reported. Statistical differences have been calculated from absolute values of each group representing at least 6–16 different determinations. The administration of each of the two hormones produced effects which were different in pregnant and cyclic females. Cortisol administration to adrenalectomized females in pro-oestrous phase or during pregnancy produced increases in glycogen reserves of all the organs except liver in pro-oestrous phase. The increase in cardiac glycogen during pro-oestrous phase after administration of cortisol was specially important (65% higher than the adrenalectomized heart in pro-oestrous phase). Similar treatment

Table 2. The effect of hypophysectomy and compensatory treatment with ACTH on glycogen stores

Treatment		Uterus	Heart	Liver
Pro-oestrous (C)	absolute value	1.2 ± 0.12 (8)*	2.34 ± 0.12 (8)	58.0 ± 3.9 (8)
Pregnant 21 days (P)	absolute value	1.44 ± 0.14 (9)	1.24 ± 0.24 (9)	34.7 ± 2.2 (9)
Hypophysectomized in Pro-oestrous (CH)	absolute value	0.86 ± 0.05 (6)	0.49 ± 0.08 (6)	23.3 ± 11.0 (6)
	% of pro-oest	72	21	40
Hypophysectomized during pregnancy (PH)	absolute value	1.7 ± 0.17 (8)	0.95 ± 0.17 (7)	34.98 ± 9.5 (8)
	% of 21d preg.	118	77	101
CH + ACTH**	absolute value	0.49 ± 0.09 (8)	1.82 ± 0.15 (8)	49.3 ± 3.6 (8)
	% of operated	57	371	211
	% of pro oest.	41	78	84
PH + ACTH**	absolute value	1.69 ± 0.15 (6)	1.65 ± 0.1 (6)	23.7 ± 4.2 (6)
	% of operated	99	174	68
	% of 21d preg.	118	133	68

Significance of difference between groups:

		Uterus	
CH	Vs	CH + ACTH	$P < 0.005$
C	Vs	CH + ACTH	$P < 0.001$
PH	Vs	PH + ACTH	Not Significant
P	Vs	PH + ACTH	Not Significant
		Heart	
CH	Vs	CH + ACTH	$P < 0.001$
C	Vs	CH + ACTH	Not Significant
PH	Vs	PH + ACTH	$P < 0.001$
P	Vs	PH + ACTH	Not Significant
		Liver	
CH	Vs	CH + ACTH	Not Significant
C	Vs	CH + ACTH	Not Significant
PH	Vs	PH + ACTH	$P < 0.02$
P	Vs	PH + ACTH	Not Significant

Figures in parenthesis represent number of animals.

* mg glycogen/g of wet weight.

** The animals were administered for 5 days with 4 IU of ACTH/rat.

of hydrocortisone to pregnant females produced increases of moderate intensities. The pre-treatment of hypophysectomized females during pregnancy with ACTH produced 74% increase in cardiac glycogen stores and 32% decrease in hepatic glycogen from non-injected hypophysectomized values. The injections of ACTH to pro-oestrous hypophysectomized females resulted in 271% and 111% increases in cardiac and hepatic glycogen respectively but this treatment declined uterine glycogen by 43%. Most of the hormonal administrations to operated rats produced effects of statistical significance which are shown in Tables 1 and 2.

DISCUSSION

The present investigation suggests that the stores of hepatic and cardiac glycogen during last part of pregnancy are lower than that of pro-oestrous phase, while on the other hand, uterine glycogen shows an opposite effect. At parturition the glycogen reserves of liver and heart increase when that of uterus decline rapidly. The increase in uterine glycogen in the last part of pregnancy is far lower than the decrease of hepatic glycogen. This difference could be due to utilization of glycogen for other needs such as accumulation in the foetal liver between 18–21 days of foetal life, since it is known that foetal liver glycogen increases 35 times during the latter interval [19, 20]. Several other mechanisms have been suggested recently to contribute to glucose lowering during pregnancy such as increased glucose transport from maternal circulation towards foetus through placenta since glucose fall is reversed by hysterectomy [21] or fetectomy [22, 23].

After comparing the present findings with our previous results regarding the alterations in plasma monoamines during the course of gestation, it can be suggested that the fall in hepatic and cardiac glycogen at 17 and 21 days post-coitum may be related to increases in total plasma monoamines [24–26]. It is apparent that uterine glycogen is protected from the glycogenolytic action of catecholamines from day 20 of pregnancy to the onset of parturition. After adrenalectomy the disappearance of two hyperglycemic agents, adrenaline and glucocorticoids, makes the interpretation difficult with respect to their function for the control of glycogen reserves in the glands studied [27–29]. It is well known that glucocorticoids stimulate hepatic glycogenesis in liver [30, 31]. Therefore adrenalectomy should result in a decrease of hepatic glycogen. However adrenalectomy can also result in increased hepatic glycogen since Sutherland and Rall [32] have shown that adrenaline is the most active catecholamine for hepatic glycogenolysis. Our results show that in pregnant and cyclic females adrenalectomy does not affect hepatic glycogen. Thus the simultaneous deprivation of both the catecholamines and glucocorticoids by complete adrenal ablation may compensate the action of each other. The situation is even more complex with cardiac and uterine glycogen since the effects of adrenalectomy are different according to the physiological state of the females. Some time ago it was also demonstrated that noradrenaline is as active as adrenaline on glycogenolysis of cardiac glycogen [27]. This evidence could be considered responsible for the important decrease in heart glycogen as adrenalectomized females in pro-oestrous phase have two-fold increase in plasma levels of noradrenaline [33]. However the same argument is not valid for females adrenalectomized during pregnancy which in spite of an increase in plasma noradrenaline show no variation in cardiac glycogen reserves. This difference in response between pro-oestrous phase and pregnancy is even more evident if one considers uterine glycogen. The observed decrease in uterine glycogen may be related to the increase of plasma noradrenaline after adrenalectomy, but under similar condition uterine glycogen of the pregnant females increases.

The glycogen stores of pregnant females show a homogenous response to cortisol resulting in increased glycogenesis. However, liver of operated females in pro-oestrous does not respond to cortisol. This observation in some way supports Exton's hypothesis [34] that the effects of corticoids on hepatic glycogen metabolism seem to be permissive rather than direct. Similar interpretation can be applied to adrenaline action on liver glycogenolysis and gluconeogenesis during pregnancy which are not direct but probably mediated by a complex hormonal participation. Recent reviews on the role of progesterone, oestrogens and placental hormones on glycogen metabolism and formation and gluconeogenesis in the rat have thoroughly analyzed all factors [35, 36]. Exogenous corticoids have also been shown to increase glucagon secretion which might explain the differences which we observe in two groups of females [37].

The effects of hypophysectomy on glycogen storage between pregnant and cyclic females could be somewhat compared to adrenalectomy. Hypophysectomy depresses adrenal steroidogenesis as well as methylation of adrenaline [38]. A tendency to develop hypoglycemia spontaneously has been widely noticed in hypophysectomized animals [39]. Generally hypophysectomized animals do not show change in glucose and glycogen contents if fed normally but even the rapid loss of carbohydrate in fasted hypophysectomized animals can be prevented by adrenocortical hormones, presumably through their property of stimulating gluconeogenesis. However pituitary extracts can stimulate normal glycogen levels during fasting even in the absence of adrenal gland, and purified growth hormone free of adrenotrophin has also been found to be active in this respect [40]. Therefore adrenal cortex appears to be in part responsible for the maintenance of normal glycogen reserves in the liver, whereas the pituitary gland may affect muscle glycogen maintenance. Important increase in glucagon and decrease in insulin contents have also been

noticed in hypophysectomized animals [41]. The variation after ACTH can be related to normal return of pancreatic hormonal secretions [41]. The present observations about hormonal deprivations and compensatory pre-treatment with ACTH and cortisol during normal life and pregnancy reflect additional role of endocrine function for the control of glycogen storage in uterus, heart and liver. Though the choice of hormones for compensatory treatments of adrenalectomized and hypophysectomized females was limited but we still observed a tendency for modification towards normal level by cyclic and pregnant females. Testing all hormones which are affected by hypophysectomy and adrenalectomy remains beyond any possible study since each gland secretes sometimes more than ten hormones. The choice of two hormones used in our study provides important evidence that ACTH and hydrocortisone, which are the essential components of hypophyseo–adrenocortical system, have a significant role for physiological and metabolic implications in the processes of carbohydrate regulation especially during late pregnancy and parturition.

Acknowledgements—The authors express their sincere thanks to S. Sohlberg, Department of Physiology, University of Gothenberg and S. A. Raza-Bukhari for their kind participation in many experiments. We are extremely indebted to Professor R. Vaillant of Paris University for the fruitful discussions and advice about the regulation of carbohydrate metabolism during pregnancy. The kind technical assistence of Miss Telliez is also acknowledged with thanks. This study was partly supported by DGRST, Section of Endocrinology of Reproduction, Paris, France.

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