C H A P T E R III

ALTERATIONS IN CARBOHYDRATE METABOLISM DUE TO INDUCED CHRONIC ADRENOCORTICAL DEFICIENCY AND EXCESS IN POST-HATCHED WHITE LEGHORN BREED OF CHICKS

Carbohydrate metabolism in adult avian forms in relation to various aspects of functioning such as growth, reproduction, and adjustments and adaptations to environmental situations has been studied in greater detail (See Hazelwood, 1986). Carbohydrate metabolism during embryonic development has also been studied to a greater detail (Romanoff, 1967; Bell and Freeman, 1984). However, its crucial significance in post embryonic development in relation to growth needs no emphasis and has received relatively lesser attention.

Dramatic changes in carbohydrate metabolism occurring during the period of transition from prenatal to neonatal stages in mammals and at about the time of hatching in the chick have been highlighted (Raheja et al., 1971a). Gluconeogenic enzymes increase in activity during the progressive development of a chick embryo and reach a maximum near the time of hatching (Okuno et al., 1964; Felicioli et al., 1967; Sheid and Hirschberg, 1967). The gluconeogenic system is poor or absent in mammalian foetal liver (Ballard and Oliver, 1963, 1965) and becomes active only after birth (Dawkins, 1963; Ballard and Hanson, 1967; Hahn and Greenberg, 1968). This is attributed to the fact that the mammalian foetus gets a constant supply of glucose from the maternal circulation thus not dependant on gluconeogenesis of its own until after birth. However, in the avian species, the embryo develops as an isolated system without a constant supply of glucose from the maternal source,

thereby necessitating active gluconeogenesis during embryonic development. Raheja et al. (1971a) based on their studies on the activities of enzymes involved in lipogenesis, gluconeogenesis and glycolysis in the chick, concluded that, gluconeogenesis is active in early life and again after maturity, whereas, lipogenesis is minimal at day one, increases rapidly during the first week and declines rapidly after 3 weeks. Apparently, the post-hatched neonatal phase of avian species is marked by adaptive metabolic shifts preparatory to the establishment of adult pattern of metabolic homeostasis. The participation of endocrine secretions in these adaptive alterations can be presumed.

The endocrine regulation of adult avian carbohydrate metabolism has received greater attention (Hazelwood, 1986). However, the regulation of carbohydrate metabolism during post-hatched development of birds has received comparatively less attention. Of the various hormones, adrenal corticosteroids have long been known to regulate glucose homeostasis and carbohydrate metabolism (Sistare and Haynes Jr., 1985). Abnormal carbohydrate metabolism has been recognized in both adrenal insufficiency (Kitabachi et al., 1968; Ivarsson et al., 1983) and hypercorticalism (Conn and Fajans, 1956; Kitabachi et al., 1973; Olefsky and Kimmerling, 1976). The present study was undertaken to investigate the effect of induced in vivo chronic adrenocortical insufficiency (by low doses of dexamethasone treatment) and adrenocortical excess (by corticosterone administration) on glycogen content and phosphorylase activity of liver, pectoralis muscle and testis, hepatic glucose-6-phosphatase (G-6-Pase) activity and, blood glucose during the first month of post-hatched development in White Leghorn breed of chicks.

MATERIAL AND METHODS

As outlined in Chapter I.

RESULTS

Blood glucose

Administration of DXM(L) and DXM(H) doses resulted in hypoglycemia in a dose dependent fashion. Corticosterone treatment was marked by significant ($P<0.001$) hyperglycemia when compared to the control. (Table 1; Fig. 1)

Glycogen content of liver, muscle and testis

The glycogen content of all the three tissues showed significant dose related increment with dexamethasone and significant decrease with corticosterone treatment.(Table 1; Fig. 1)

Phosphorylase activity of liver, muscle and testis

The total phosphorylase activity in all the three tissues decreased significantly with both DXM(L) and DXM(H). Corticosterone treatment significantly increased the enzyme activity in both liver and muscle while in the testis there was no significant change from the control value.(Table 2; Fig. 2)

Hepatic Glucose-6-phosphatase (G-6-Pase)

The hepatic G-6-Pase activity increased significantly in both corticosterone and dexamethasone treated chicks.(Table 2; Fig. 2)

Table 1 Glycogen contents of liver, muscle and testis and blood glucose of chicks treated with dexamethasone and corticosterone for 30 days.

	Blood glucose mg/100 ml blood	Glycogen mg/100 mg tissue		
		LIVER	MUSCLE	TESTIS
CONTROL	222.77 ±3.19	2.513 ±0.215	0.667 ±0.040	0.0461 ±0.0024
DXM(L)	191.18[a] ±5.11	3.42[b] ±0.14	0.831[b] ±0.028	0.0608[b] ±0.0037
DXM(H)	179.05[a] ±5.26	5.69[a] ±0.35	1.089[a] ±0.072	0.0632[b] ±0.0034
CORT	244.20[a] ±4.86	1.12[a] ±0.22	0.526[c] ±0.033	0.0225[a] ±0.0011

DXM(L) : dexamethasone low dose; DXM(H) : dexamethasone high dose
CORT : corticosterone
Values are mean ±SE of not less than 8 birds.
a : $P < 0.001$; b : $P < 0.01$; c : $P < 0.02$

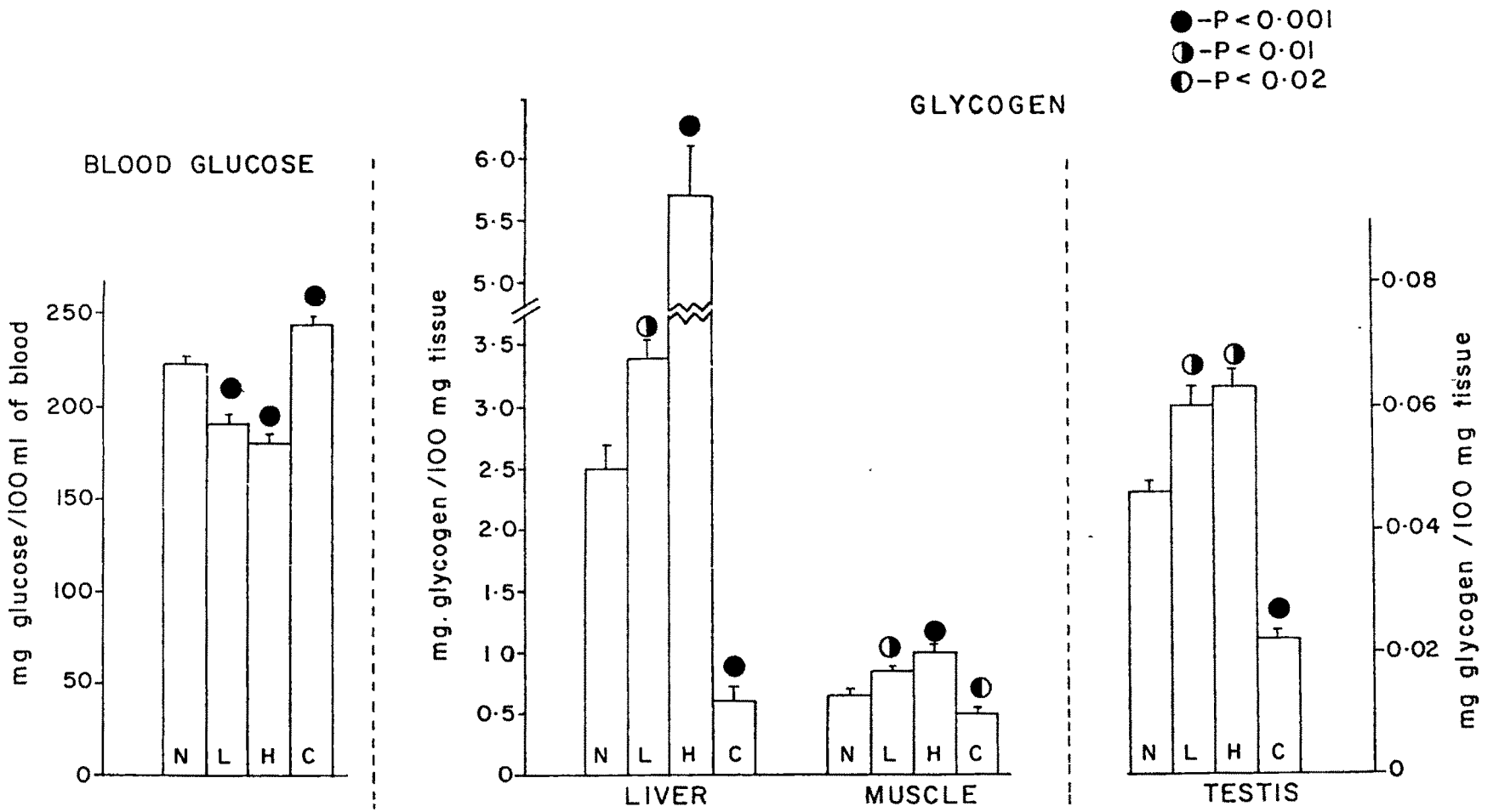

Fig. 1 Blood glucose levels and glycogen content in liver, muscle and testis of normal (N), dexamethasonised (L and H) and corticosterone treated chicks.

Table 2 Activity levels of phosphorylase in liver, muscle and testis and hepatic glucose-6-phosphatase of chicks treated with dexamethasone and corticosterone for 30 days.

	G-6-Pase μ moles PO_4 released/mg protein/15 min.	Phosphorylase μg PO_4 released/mg protein/30 min.		
		LIVER	MUSCLE	TESTIS
CONTROL	0.893 ±0.052	22.34 ±1.78	20.87 ±1.57	89.48 ±6.20
DXM(L)	1.087^{c} ±0.068	14.15^{b} ±1.54	14.88^{b} ±1.03	19.83^{a} ±1.29
DXM(H)	1.206^{b} ±0.081	12.31^{a} ±0.96	15.34^{b} ±0.86	33.71^{a} ±0.93
CORT	1.763^{a} ±0.123	41.36^{a} ±4.79	49.52^{a} ±4.48	96.56 ±4.15

DXM(L) : dexamethasone low dose; DXM(H) : dexamethasone high dose
CORT : corticosterone
Values are mean ±SE of not less than 8 birds.
a : $P < 0.001$; b : $P < 0.01$; c : $P < 0.02$

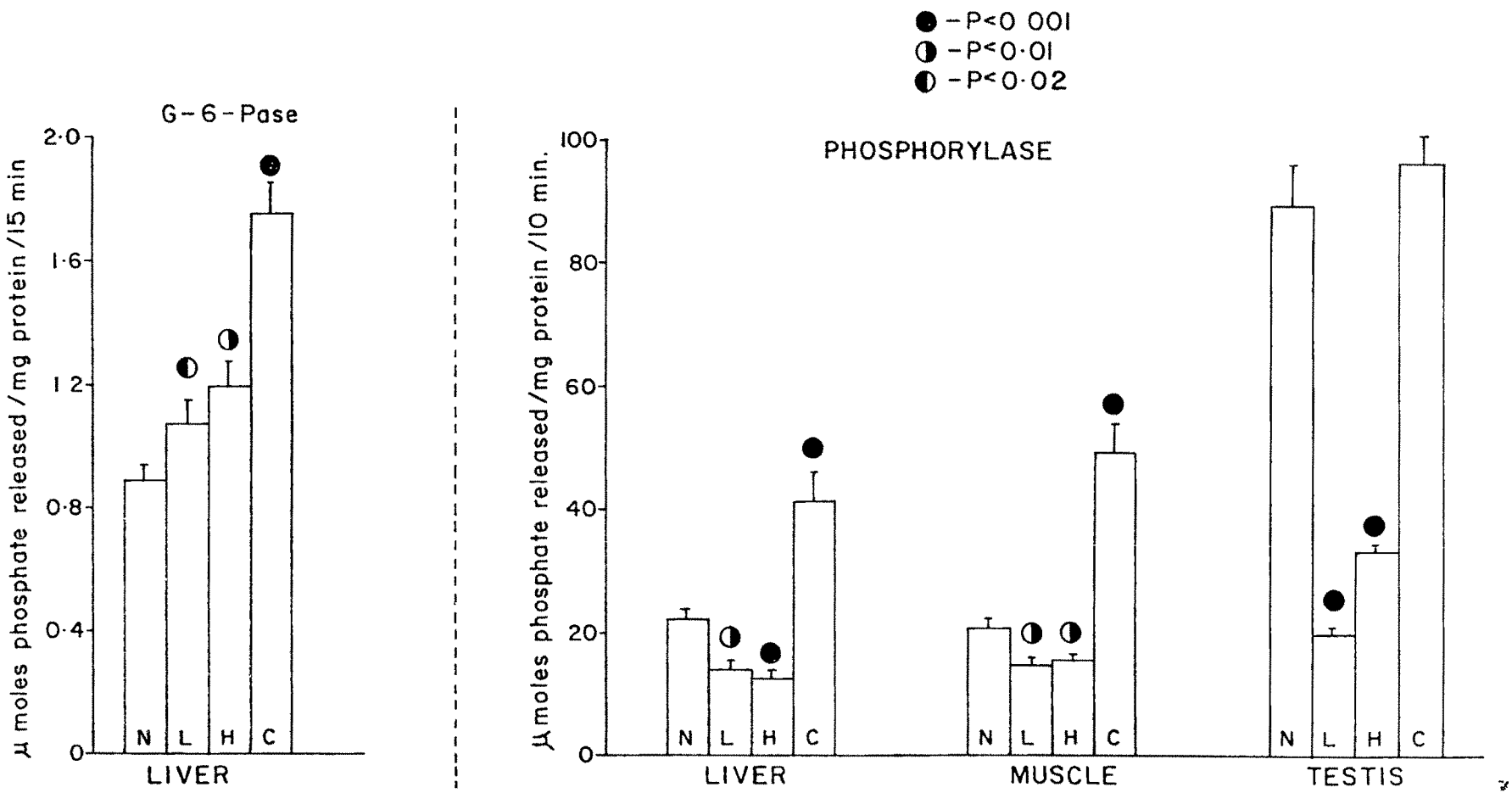

Fig. 2 Activity levels of G-6-Pase in liver and phosphorylase in liver, muscle and testis of normal (N), dexamethasonised (L and H) and corticosterone (C) treated chicks.

DISCUSSION

It is well established that the immediate post-hatched phase of chick development (3-4 weeks) is essentially marked by increased lipogenesis with concomitantly reduced gluconeogenesis, unlike in the case of mammals (Raheja et al., 1971a). However, the importance of carbohydrate metabolism during this phase of development cannot be underestimated; as during this period, the chicks feed on a high carbohydrate diet. Moreover, the essential precursors of lipogenesis are carbohydrate moieties. It is well known that major endocrine principles involved in the regulation of carbohydrate metabolism are the pancreatic hormones, the thyroid hormones and the adrenal hormones. In the case of birds, the role of pancreatic hormones has been studied to a greater extent in relation to that of thyroid and adrenal hormones. There is considerable evidence for the involvement of adrenocortical hormones in the control of carbohydrate metabolism in several vertebrate classes (Martin, 1961). Glucocorticoid treatments have been reported to result in hyperglycemia and/or glycogen deposition in birds (Greenman and Zarrow, 1961; Snedecor et al., 1963; Saadoun et al., 1987), reptiles (Coulson and Hernandez, 1953; Callard and Chan, 1972; Gist, 1978; Vasumathi and Rangnekar, 1986), amphibians (Hunter and Johnson, 1960) and teleosts (Nace, 1955; Oguri and Nace, 1966; Swallow and Fleming, 1970; Chan and Woo, 1978).

The present study undertaken essentially to evaluate the effect of chronic adrenocortical manipulation and carbohydrate metabolism during the first 30 days of neonatal life has provided evidences for the important role of corticosteroids in maintaining metabolic homeostasis

by its possible interactions with pancreatic hormones. Daily corticosterone administration resulted in marked hyperglycemia and glycogenolysis in liver, muscle and testis. In the light of the known gluconeogenic role of corticosterone, the observed hyperglycemia is understandable. The gluconeogenic action of corticosterone is supported by the enhanced G-6-Pase activity and protein catabolism (Chapter IV). However, the observed glycogen depletion is in striking contrast to the purported glycogenic effect of corticosterone. The increased phosphorylase activity in liver, muscle and testis provides strong correlation to the depleted glycogen contents in them and lends credence to increased glucagon mediated effect. The increased glucagon action in chicks treated with corticosterone may result from an altered insulin: glucagon molar ratio. Such an alteration can occur either by increased glucagon secretion/action and/or decreased insulin secretion/action. Evidences are available in this context for potentiation of glucagon action (Exton et al., 1973; O'Neill and Langslow, 1978) and glucagon release (Marco et al., 1972; O'Neill and Langslow, 1978) as well as insulin antagonism (Pierluissi et al., 1986; Natarajan et al., 1987) by glucocorticoids. It is conceivable from the present observations that chronic treatment with physiological doses of corticosterone (simulating adrenocortical excess) in the early neonatal period of chick development can result in suppression of glycogenesis coupled with activation of glycogenolysis and gluconeogenesis by creating a physiological state of hypo-insulinaemia and increased glucagon action.

The collateral study of chronic treatment with dexamethasone has given a reverse set of changes in the form of decreased phosphorylase

activity, glycogen deposition and hypoglycemia. These, very pertinently suggest a state of hypocorticalism and can be justified by the well documented inhibitory effect of dexamethasone on synthesis and release of ACTH (Kendall and Allen, 1968; Russel et al., 1969; Macharg et al., 1985; Smoak and Birrenkott, 1986; Carnes et al., 1987; De Greef and Van der Schoot, 1987; Katano, 1988). Continuing in the same theme of discussion, it is logical to presume that chronic dexamethasone treatment in the early neonatal period of chick development can create a physiological state of adrenocortical insufficiency. Apparently, a reduced titre of endogenous corticosterone would alter the existing normal homeostatic interaction with pancreatic hormones. As a consequence, the prevailing balance of insulin antagonism and glucagon potentiation due to endogenous glucocorticoid becomes minimised thereby increasing the insulin:glucagon molar/activity ratio. Obviously, in dexamethasone treated chicks, increased hepatic and peripheral uptake of glucose and glycogen deposition can be expected as is revealed by the hypoglycemic condition, decreased phosphorylase activity and increased glycogen content. In this context, Klepac (1986) has documented dexamethasone induced increased glycogen accumulation in the foetal liver, heart, adrenal and thymus of rat.

The present observations also suggest that in birds, dexamethasone, a synthetic corticosteroid, does not or cannot mimic the actions of native corticosteroid on carbohydrate metabolism unlike in mammals where dexamethasone is known to mimic the actions of corticosterone (Stillman et al., 1977; Harrelson and Mc Ewen, 1987). However, the

herein observed increased G-6-Pase activity even in dexamethasone treated chicks suggests a similarity of action in inducing G-6-Pase activity. This similarity of action may be explained by the reported ability of glucocorticoids to increase the activity of G-6-Pase by a probable translocation of the enzyme from the rough endoplasmic reticulum, thereby changing either the physical state of the protein or the microenvironment (Ballard, 1979). In this respect, dexamethasone might be mimicking the action of glucocorticoid at the cytosolic level without undergoing nuclear translocation or even if translocated not able to mimic the actions of glucocorticoid at the genic level.

It may be concluded from the present results that in neonatal chicks, glucocorticoids play an important role in regulating carbohydrate metabolism by their homeostatic interactions with pancreatic hormones.