CHAPTER – 11

NEONATAL MELATONIN ADMINISTRATION PREDISPOSES ADULT RATS TO INSULIN RESISTANCE AND DEVELOPMENT OF DIABETES DUE TO WEANING ALLOXAN TREATMENT.

INTRODUCTION:

Diabetes mellitus, whether type I (insulin dependent diabetes mellitus; IDDM) or type 2 (non-insulin dependent diabetes mellitus; NIDDM) results from an inadequate mass of functional pancreatic B cells. In the first case, the B cell mass is reduced by the autoimmune destruction of the B cells, while, in the latter, there is incomplete compensation to meet the demand often imposed by insulin resistance. Experimental evidence from rodents showed that there is substantial compensatory effort by the B cells to maintain normal glycemic levels in the face of obesity and insulin resistance Two types of compensation can occur: a functional one in which each B cell secretes more insulin and a second one in which there is a change in B cell mass. Functional adaptations, such as the changes in threshold for glucose induced insulin secretion that occur during pregnancy (Sorenson *et al.*, 1987) and glucose induced increase in glucokinase activity (Chen *et al.*, 1994), are also involved in the maintenance of

glucose homeostasis. Nonetheless, the B cell mass itself is the major factor in the amount of insulin that can be secreted, and experimental evidence clearly shows that B cell mass can increase or decrease. Thus, a better understanding of the regulation of the islet growth and development after birth many provide important new strategies for the therapy of diabetes. Increase in B cell mass may occur by different means like increased B cell replication, increased B cell size, decreased B cell death and differentiation of B cell progenitors including neogenesis (Finegood *et al.*, 1995). Neogenesis is an important aspect of B cell mass expansion during development and has been shown to contribute to increases in B cell mass in juvenile and adult rodent models (Finegood *et al*, 1995; Rosenberg, 1995; Bouwens and Kloppel, 1996). Experimental animal models of diabetes are commonly used for studying various aspects of diabetes. Alloxan, 5,6 dioxy uracil, is a potent diabetogenic agent by its B cell damaging influence, increased generation of reactive oxygen species and hydroxyl radicals is a major mechanism by which alloxan causes B cell destruction and diabetes (Bromme *et al.*, 1999; Szkudelski, 2001)

Melatonin, the pineal gland hormone acts as an endogenous synchronizer coordinating biological rhythms (Humlova Illnerova, 1990). Its function as a free radical scavenger was first suggested by Ianas *et al*, (1991). Subsequently it has been shown as a potent free radical scavenger and antioxidant (Abuja *et al.*, 1997; Qi *et al.*, 1997; Reiter *et al*, 1998). Melatonin has been shown to scavenge the most

reactive and cytotoxic oxygen species (Reiter *et al.*, 2000) and the hydroxyl radical (Tan *et al.*, 1993; Reiter *et al.*, 1997, 1998; Bromme *et al.*, 2000; Ebelt *et al.*, 2000). Melatonin has also been known to scavenge the peroxyl radical (Pieri *et al.*, 1994), the peroxy nitrite anion (Gilad *et al.*, 1997), the nitric oxide (Noda *et al.*, 1999) and the singlet oxygen (Cagnoli *et al* , 1995). It is also known to stimulate antioxidant enzymes as super oxide dismutase, glutathione peroxidase and glutathione reductase as well as inhibit the pro-oxidative enzyme, nitric oxide synthetase (Reiter *et al.*, 1998)

Previous studies have tried to evaluate the immediate and long term effects of neonatal melatonemic rats (nMT) on the immediate weaning and long term pubertal and adult metabolic features (Chapter 1-9). A favorable influence of nMT on insulin sensitivity and insulin induced oxidation potential has been noted and hence it was thought pertinent to study the influence of nMT on long term adult (60 days) on histological features of pancreas and carbohydrate, lipid and protein metabolic profiles in relation to alloxan administration at the weaning age (22 days). This study was thought justified as neonatal streptozotocin and alloxan administration have been shown to create hyperglycemia and insulin resistance in the adult stage as long term influences with a near-normal recovery in between. In this context the present study evaluates tissue glycogen, lipid and protein contents, enzymes of glycogen metabolism and serum glucose and lipid profiles as well as the histological observations of the pancreas in 60 day old

rats subjected to weaning alloxan challenge with neonatal melatonin treatment or no treatment.

MATERIAL AND METHODS: See page numbers 16-37.

RESULTS:

Body and organ weights: The CA(100) and MA(100) rats showed significantly decreased body weight as compared to MA(150) and control rats however, there is no significant difference in the body weight of MA(150) and control rats. The relative weight of pancreas of MA(100) rats increased significantly as compared to all other groups. The relative weight of liver of MA(150) rats decreased significantly as compared to MA(100) rats. The relative weight of spleen of MA(150), MA(100) and control rats decreased significantly as compared to CA(100) and nMT rats. The relative weight of kidney of MA(150), CA(100) and MA(100) rats decreased significantly as compared to control rats while, the relative weight of testes and adrenal in all the groups showed no significant alterations (Figure and Table; 11.1-11.13).

Serum glucose and insulin levels: The serum glucose level of MA(150) and MA(100) rats increased significantly as compared to nMT and control rats while, the serum insulin level of MA(150), CA(100) and MA(100) rats increased significantly as compared to nMT and control rats (Figure and Table; 11.16, 11.35).

Hepatic glycogen content and the activities of glycogen synthetase, glycogen phosphorylase and glucose-6-phosphatase: The MA(150), CA(100) and MA(100) rats showed significantly

decreased glycogen content as compared to nMT and control rats however, the glycogen content of MA(150) and MA(100) rats was significantly decreased as compared to CA(100) rats. The glycogen synthetase activity in MA(150), CA(100) and MA(100) rats decreased significantly as compared to nMT rats while, the glycogen phosphorylase activity of MA(100) rats decreased significantly as compared to all other groups. The glucose-6-phosphatase activity of CA(100) and MA(100) rats decreased significantly as compared to MA(150), nMT and control rats (Figure and Table; 11.14, 11.17, 11.19, 11.21).

Muscle glycogen content and the activities of glycogen synthetase and glycogen phosphorylase: The MA(150) and MA(100) rats showed significantly decreased glycogen content as compared to CA(100), nMT and control rats. Also the activity of glycogen synthetase was significantly decreased in MA(150), CA(100) and MA(100) rats as compared to nMT rats. The glycogen phosphorylase activity did not show any significant alteration except for a significant decrease in MA(100) rats compared to CA(100) rats (Figure and Table; 11.15, 11.11.18, 11.20).

Hepatic and muscle protein content: The MA(100) rats showed significantly increased hepatic and muscle protein content as compared to MA(150), CA(100), nMT and control rats (Figure and Table; 11.22, 11 23).

Hepatic total lipid and cholesterol content: The hepatic total lipid content of MA(150) and MA(100) rats was significantly increased as

compared to CA(100) rats but showed no significant alteration with control rats. The hepatic cholesterol content of MA(100) rats increased significantly as compared to all other groups (Figure and Table; 11.24, 11.25).

Muscle total lipid and cholesterol content: The muscle total lipid and cholesterol content of MA(100) rats decreased significantly as compared to all other groups(Figure and Table; 11 26, 11 27).

.**Adipose tissue total lipid and cholesterol content:** The adipose tissue total lipid content of MA(100) and CA(100) rats decreased significantly as compared to MA(150) and control rats but were increased as compared to nMT rats The adipose tissue cholesterol content of MA(150), CA(100), MA(100) and control rats decreased significantly as compared to nMT rats (Figure and Table; 11.28, 11.29).

Serum lipid fractions: The serum triglyceride level of MA(150), CA(100) and MA(100) rats decreased significantly as compared to control rats while, the serum cholesterol level of MA(100) rats increased significantly as compared to MA(150), CA(100), nMT and control rats. The serum total lipid level of MA(150), CA(100), MA(100) rats decreased significantly as compared to control rats while, the serum phospholipid level of MA(100) rats decreased significantly as compared to MA(150), CA(100) and control rats. The serum free fatty acid level of MA(100) rats decreased significantly as compared to all other groups (Figure and Table; 11.30, 11.31, 11.32, 11.33, 11.34).

Figure 11.1: Body weight of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

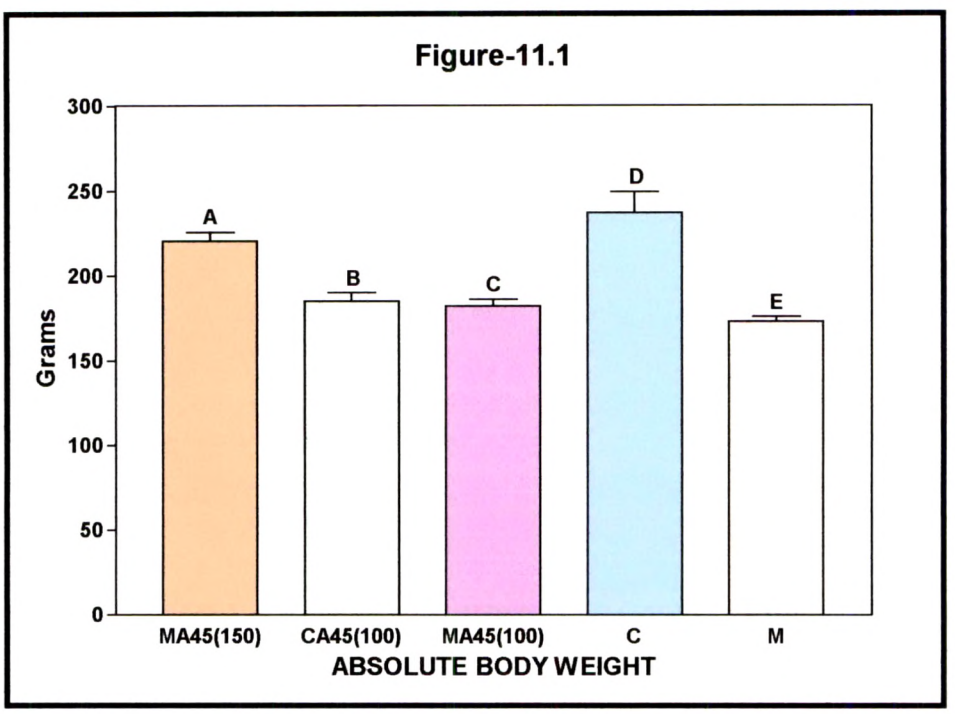


Table 11.1: Body weight of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)[A]	CA(100)[B]	MA(100)[C]	C[D]	M[E]
BODY WEIGHT	220.70 ±4.70	185.00 ±5.01	182.00 ±4.00	237.25 ±12.38	173.00 ±3.00

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	●	■	NS	■	NS	◆	NS	◆	NS	◆

Values are expressed as mean ± SEM, ◆p<0.001; ■P<0.01; ●P<0.05;
NS Non Significant

Figure 11.2: Absolute weight of pancreas of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

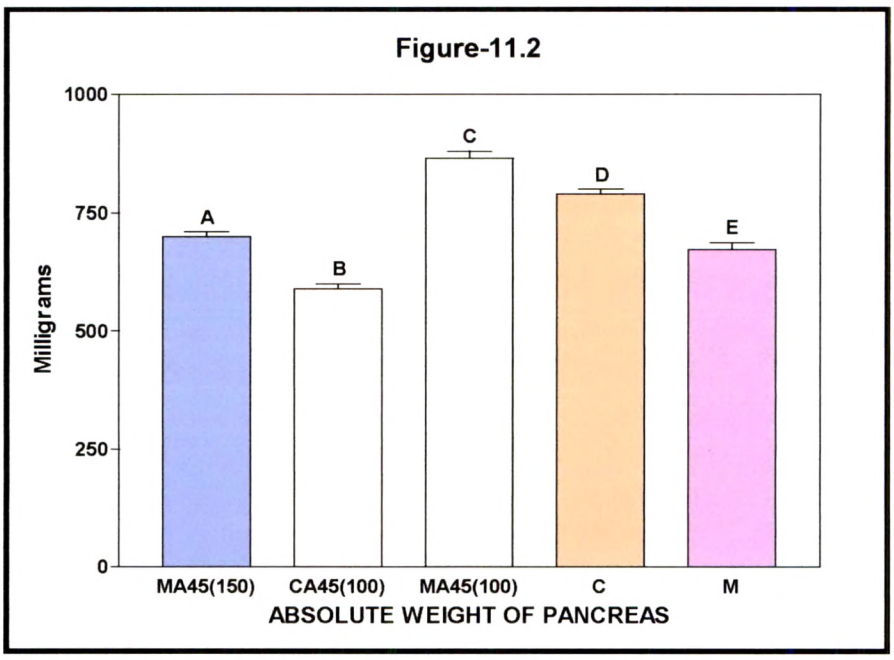


Table 11.2: Absolute weight of pancreas of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
PANCREAS	700.00 ±10.02	590.00 ±10.02	865.00 ±15.04	790.00 ±10.02	672.25 ±14.78

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	◆	◆	■	NS	◆	◆	■	■	◆	◆

Values are expressed as mean ± SEM, ◆p<0.001; ■P<0.01; NSNon Significant

Figure 11.3: Absolute weight of liver of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

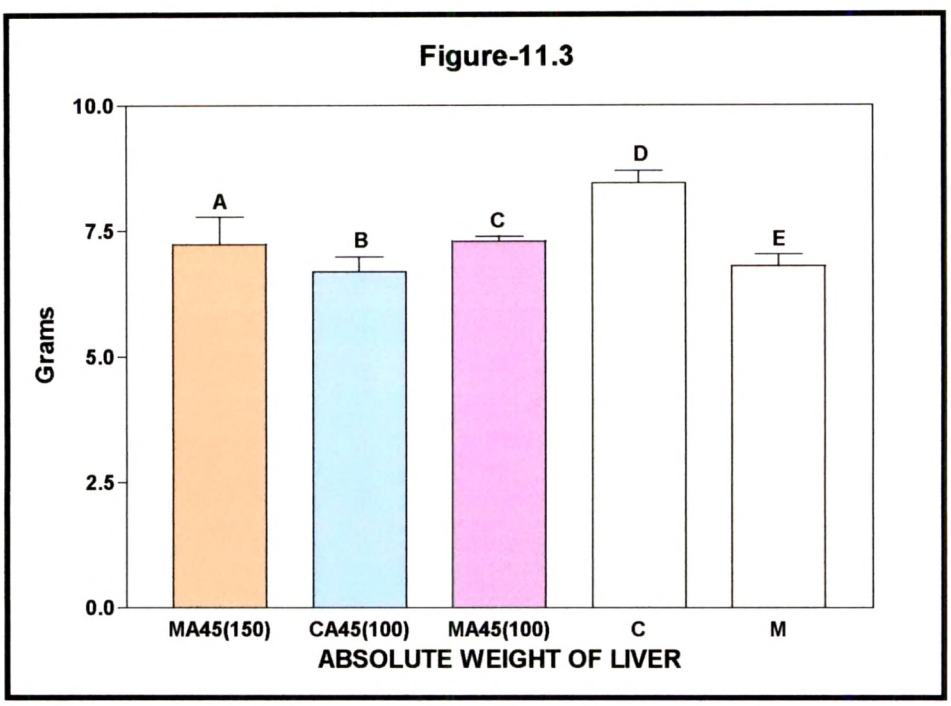


Table 11.3: Absolute weight of liver of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
LIVER	7.24 ±0.54	6.70 ±0.29	7.30 ±0.099	8.46 ±0.24	6.81 ±0.23

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	NS	NS	NS	NS	•	NS	NS	NS	•

Values are expressed as mean ± SEM, •P<0.05; NSNon Significant

Figure 11.4: Absolute weight of spleen of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

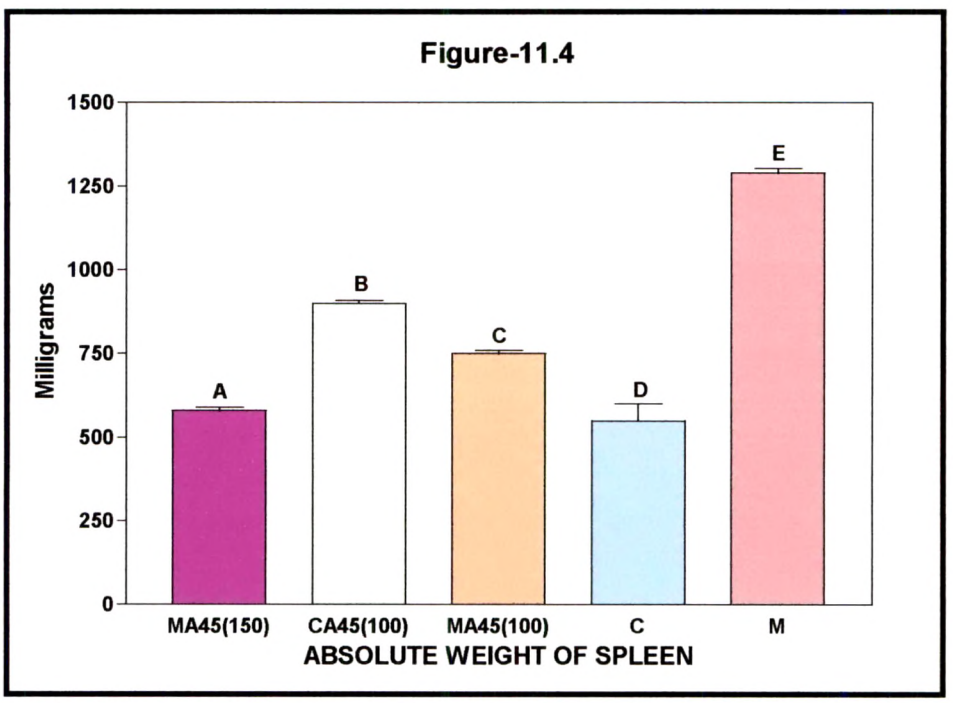


Table 11.4: Absolute weight of spleen of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
SPLEEN	580.00 ±10.02	900.00 ±9.90	750.00 ±10.02	550.00 ±50.14	1290.00 ±14.00

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	◆	■	NS	◆	■	◆	◆	◆	◆	◆

Values are expressed as mean ± SEM, ◆p<0.001; ■P<0.01;
NS Non Significant

Figure 11.5: Absolute weight of kidney of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

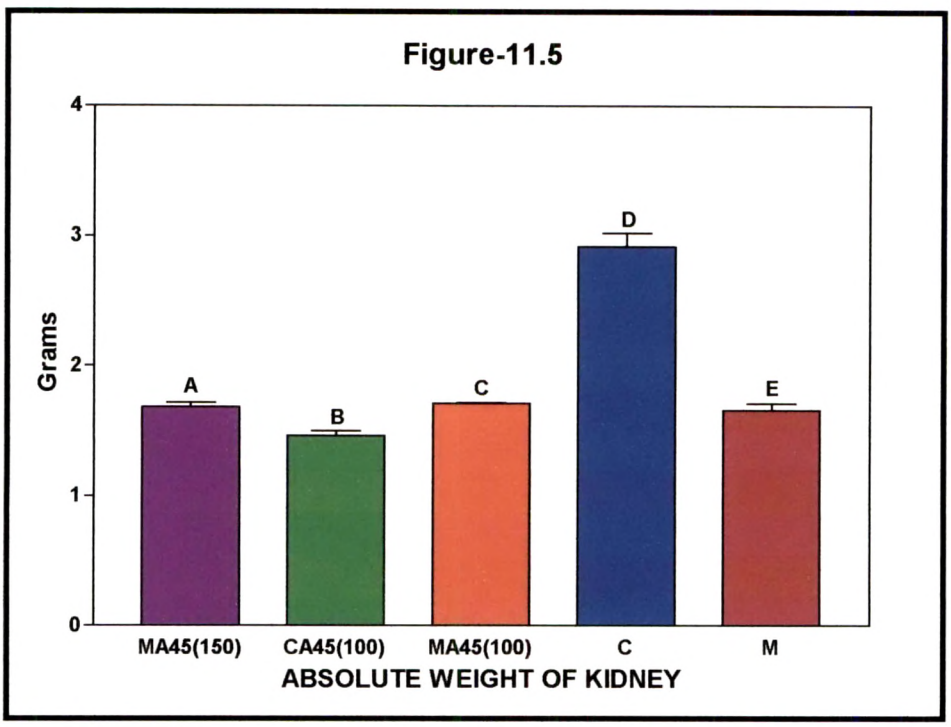


Table 11.5: Absolute weight of kidney of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
KIDNEY	1.68 ±0.034	1.46 ±0.039	1.71 ±0.004	2.92 ±0.10	1.66 ±0.049

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	NS	◆	NS	NS	◆	NS	◆	NS	◆

Values are expressed as mean ± SEM, ◆p<0.001; NS Non Significant

Figure 11.6: Absolute weight of testes of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

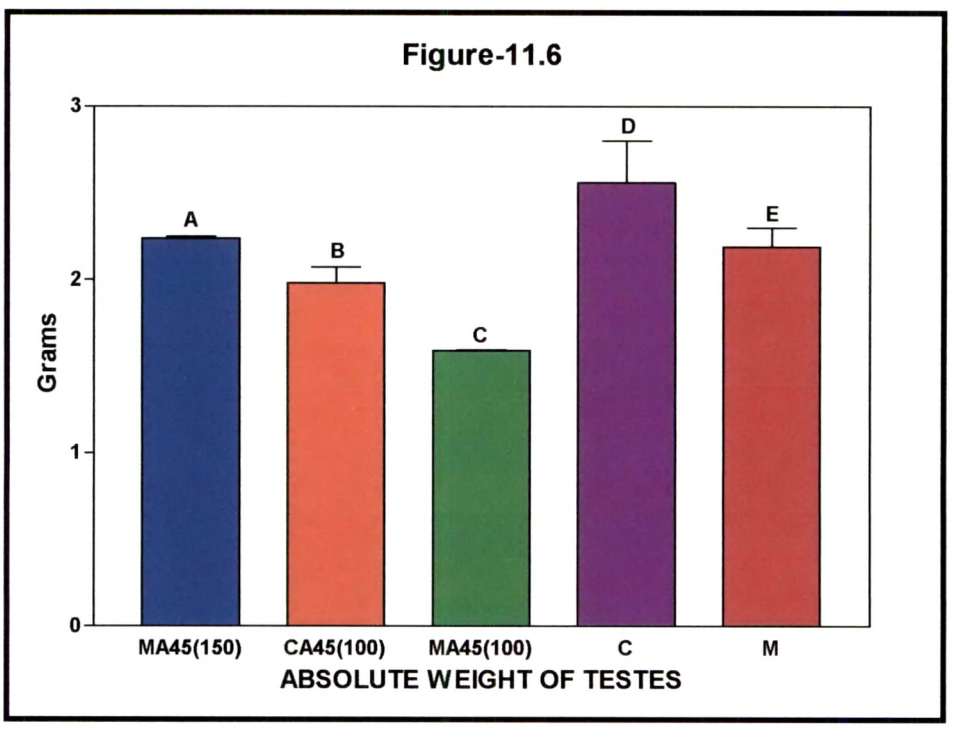


Table 11.6: Absolute weight of testes of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
TESTES	2.24 ±0.092	1.98 ±0.092	1.59 ±0.004	2.56 ±0.24	2.19 ±0.11

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	●	NS	NS	NS	NS	NS	◆	●	NS

Values are expressed as mean ± SEM, ◆p<0.001; ●P<0.05;
NSNon Significant

Figure 11.7: Absolute weight of adrenal of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

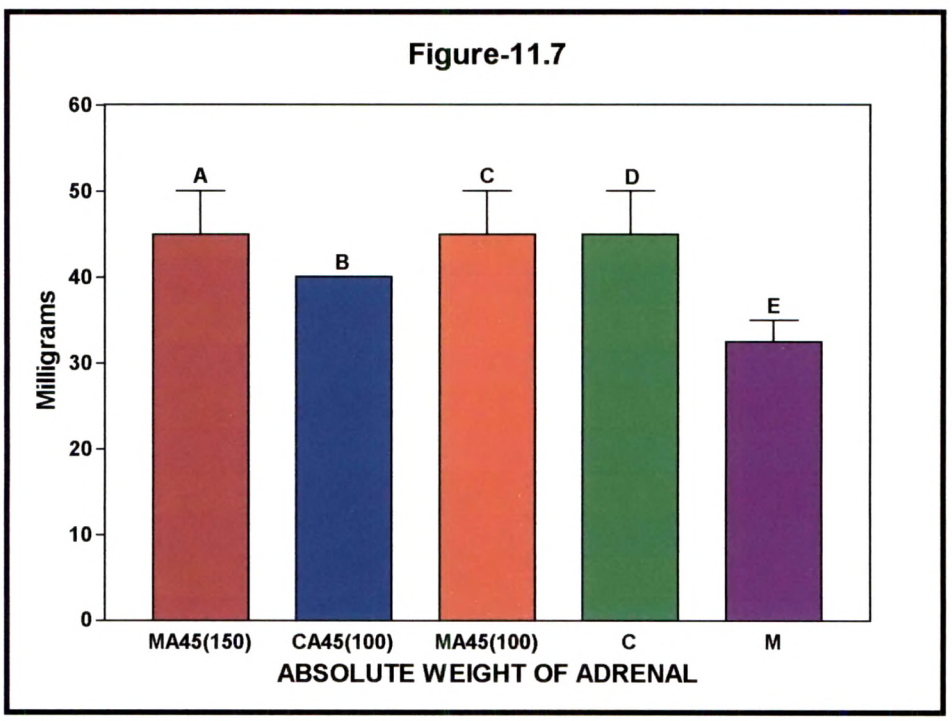


Table 11.7: Absolute weight of adrenal of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
ADRENAL	45.00 ±5.01	40.00 ±0.08	45.00 ±5.01	45.00 ±5.01	32.50 ±2.5

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Values are expressed as mean ± SEM, NSNon Significant

Figure 11.8: Relative weight of pancreas of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

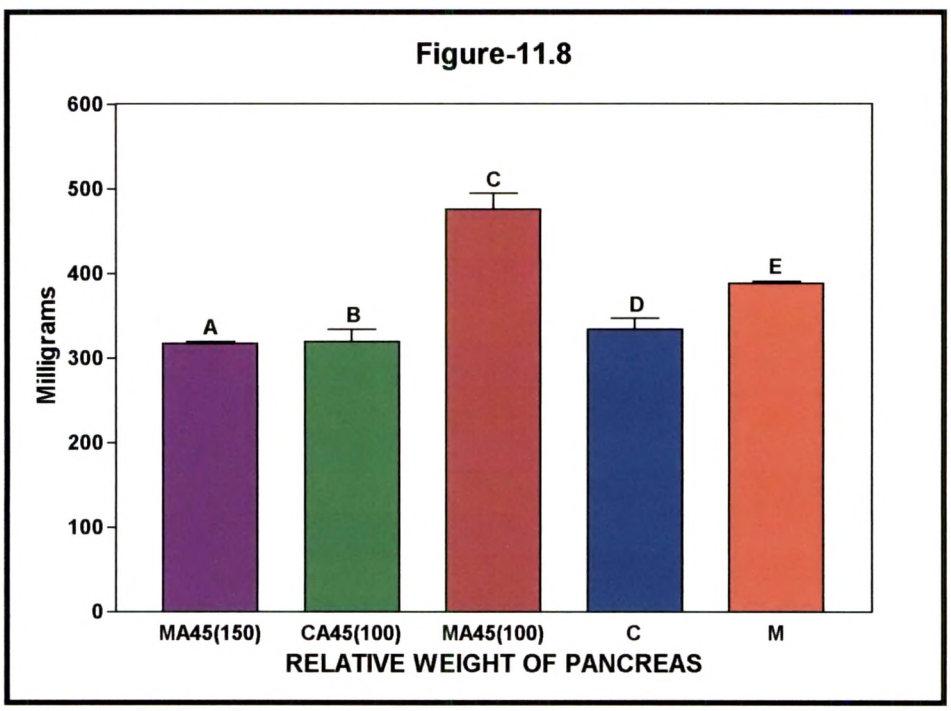


Table 11.8: Relative weight of pancreas of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
PANCREAS	317.21 ±2.22	319.29 ±2.78	475.68 ±18.75	333.66 ±13.19	388.55 ±1.79

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	◆	NS	■	◆	NS	●	◆	■	NS

Values are expressed as mean ± SEM, ◆p<0.001; ■P<0.01; ●P<0.05; NSNon Significant

Figure 11.9: Relative weight of liver of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

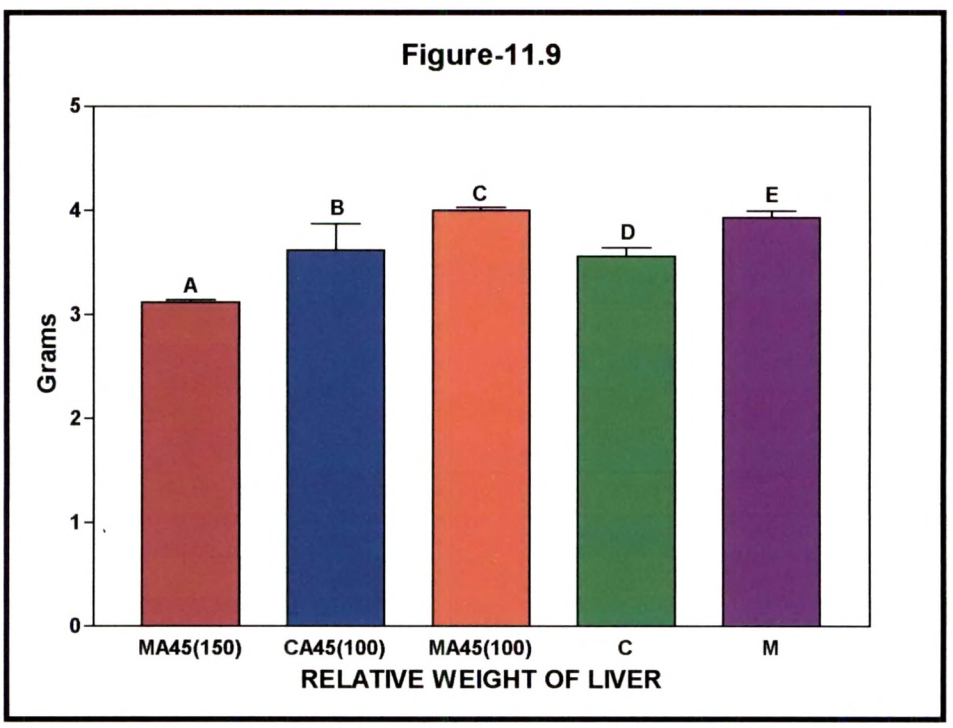


Table 11.9: Relative weight of liver of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
LIVER	312 ±0.019	3.62 ±0.25	4.00 ±0.034	3.56 ±0.085	3.93 ±0.064

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	■	NS	■	NS	NS	NS	NS	NS	NS

Values are expressed as mean ± SEM, ■P<0.01; NSNon Significant

Figure 11.10: Relative weight of spleen of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

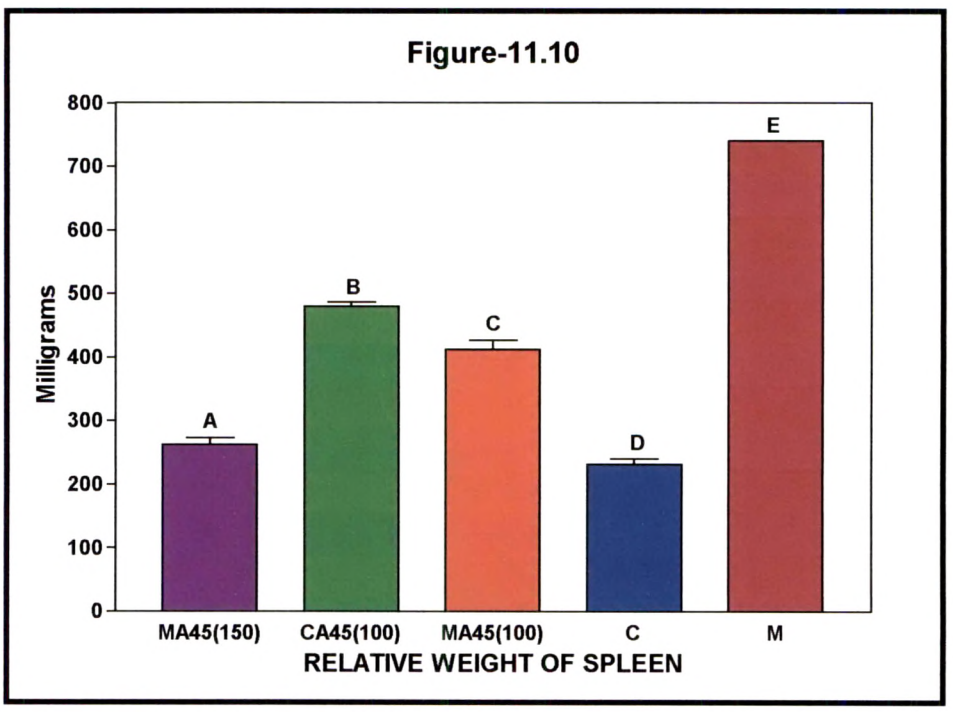


Table 11.10: Relative weight of spleen of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
SPLEEN	263.01 ±10.15	480.00 ±6.40	412.4 ±14.55	231.35 ±9.05	740.00 ±0.99

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	◆	◆	NS	◆	■	◆	◆	◆	◆	◆

Values are expressed as mean ± SEM, ◆p<0.001; NSNon Significant

Figure 11.11: Relative weight of kidney of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

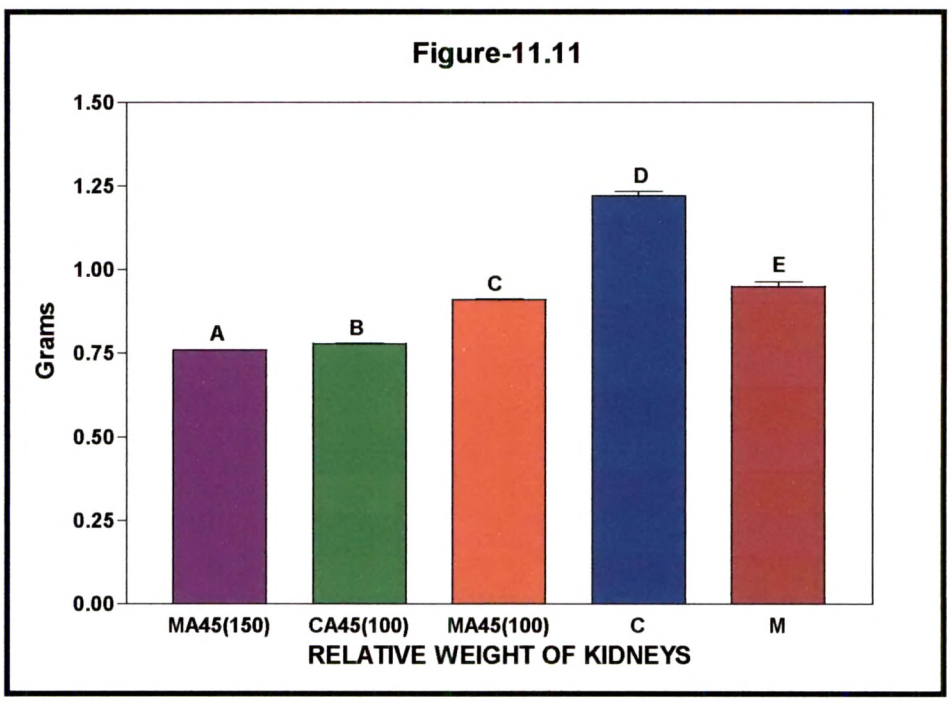


Table 11.11: Relative weight of kidney of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
KIDNEY	0.76 ±0.001	0.78 ±0.001	0.91 ±0.024	1.22 ±0.014	0.95 ±0.014

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	◆	◆	◆	◆	◆	◆	◆	NS	◆

Values are expressed as mean ± SEM, ◆p<0.001; NSNon Significant

Figure 11.12: Relative weight of testes of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

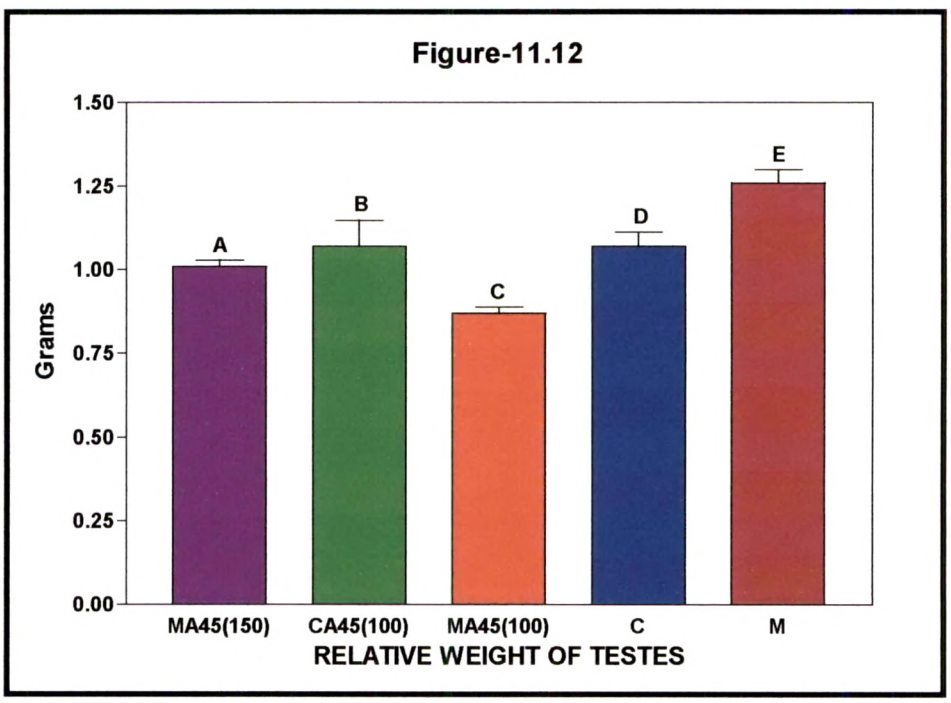


Table 11.12: Relative weight of testes of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
TESTES	1.01 ±0.019	1.07 ±0.078	0.87 ±0.019	1.07 ±0.042	1.26 ±0.04

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	NS	NS	●	NS	NS	NS	NS	◆	NS

Values are expressed as mean ± SEM, ◆p<0.001; ●P<0.05;
NS Non Significant

Figure 11.13: Relative weight of adrenal of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

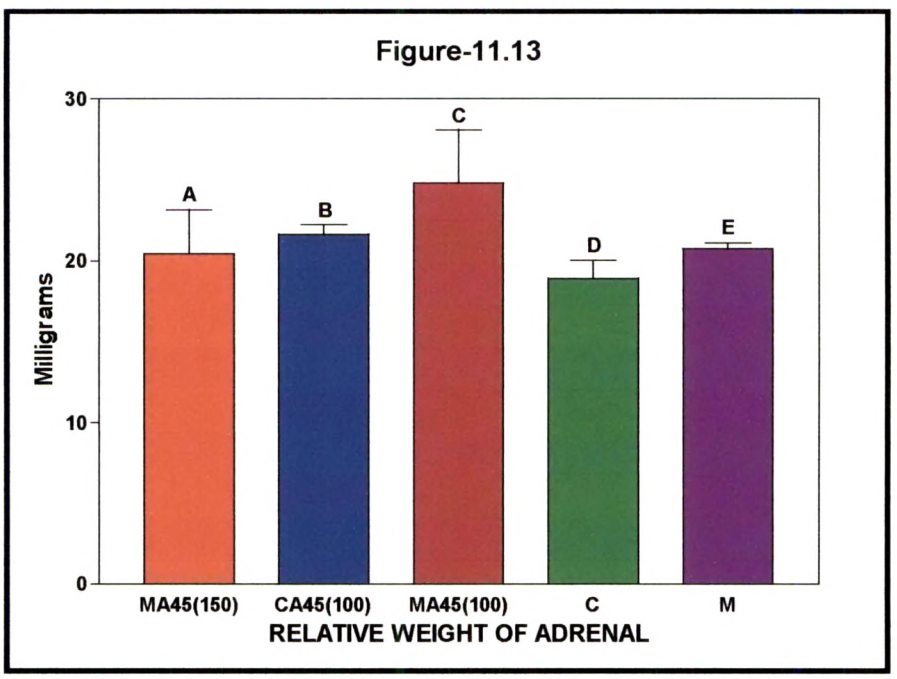


Table 11.13: Relative weight of adrenal of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
ADRENAL	20.44 ±2.70	21.63 ±0.58	24.79 ±3.29	18.90 ±1.12	20.73 ±0.34

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Values are expressed as mean ± SEM, NS Non Significant

Figure 11.14: Hepatic glycogen content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

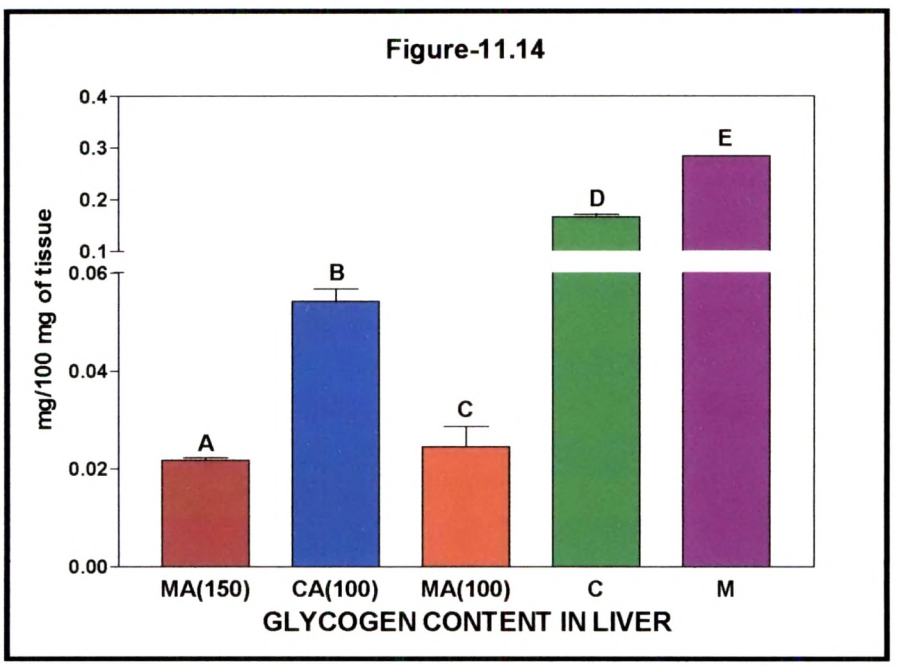


Table 11.14: Hepatic glycogen content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
GLYCOGEN	0.0217 ±0.00055	0.0541 ±0.002549	0.0245 ±0.00408	0.1672 ±0.0048	0.2846 ±0.00041

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	◆	NS	◆	◆	◆	◆	◆	◆	◆	◆

Values are expressed as mean ± SEM, ◆p<0.001; NSNon Significant

Figure 11.15: Muscle glycogen content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

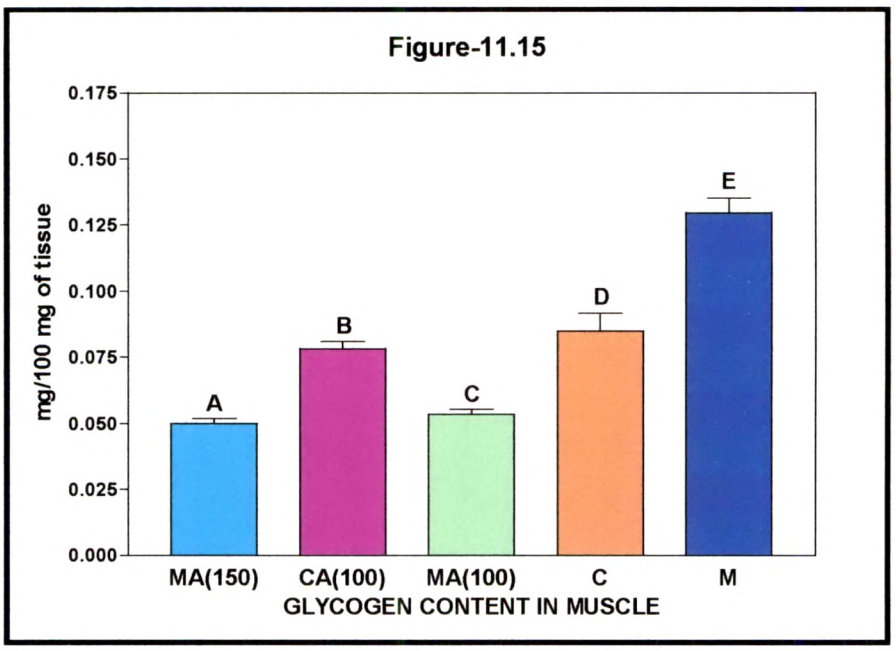


Table 11.15: Muscle glycogen content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
GLYCOGEN	0.050 ±0.00185	0.0783 ±0.00264	0.0536 ±0.00177	0.0848 ±0.0069	0.1297 ±0.0055

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	◆	NS	◆	◆	◆	NS	◆	◆	◆	◆

Values are expressed as mean ± SEM, ◆p<0.001; NSNon Significant

Figure 11.16: Serum glucose level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

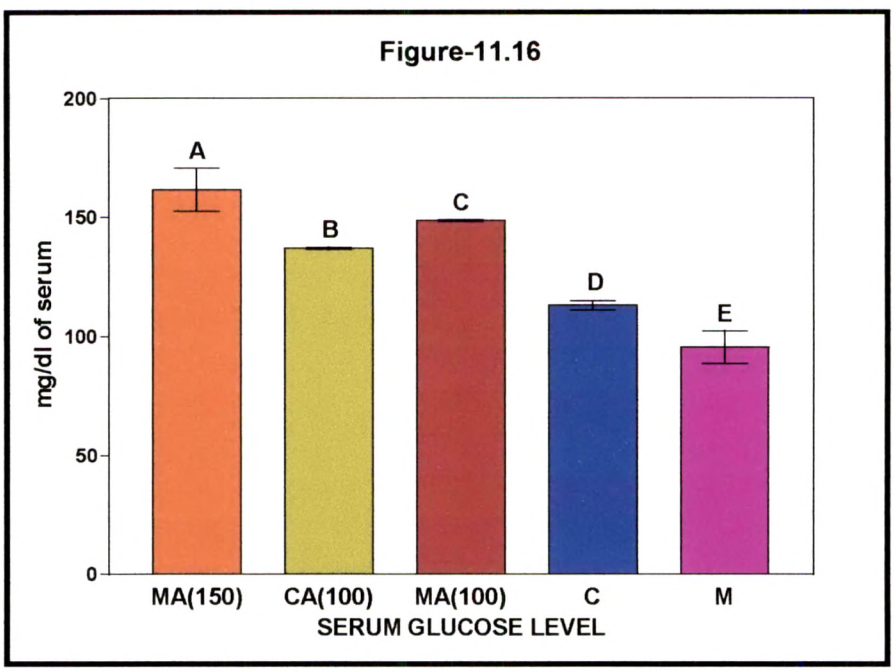


Table 11.16: Serum glucose level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
GLUCOSE	161.76 ±9.0044	137.07 ±0.4956	148.74 ±0.3964	113.15 ±1.9210	95.57 ±6.8375

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	NS	◆	◆	NS	NS	◆	■	◆	NS

Values are expressed as mean ± SEM, ◆p<0.001; ■P<0.01; NSNon Significant

Figure 11.17: Hepatic glycogen synthetase activity in adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

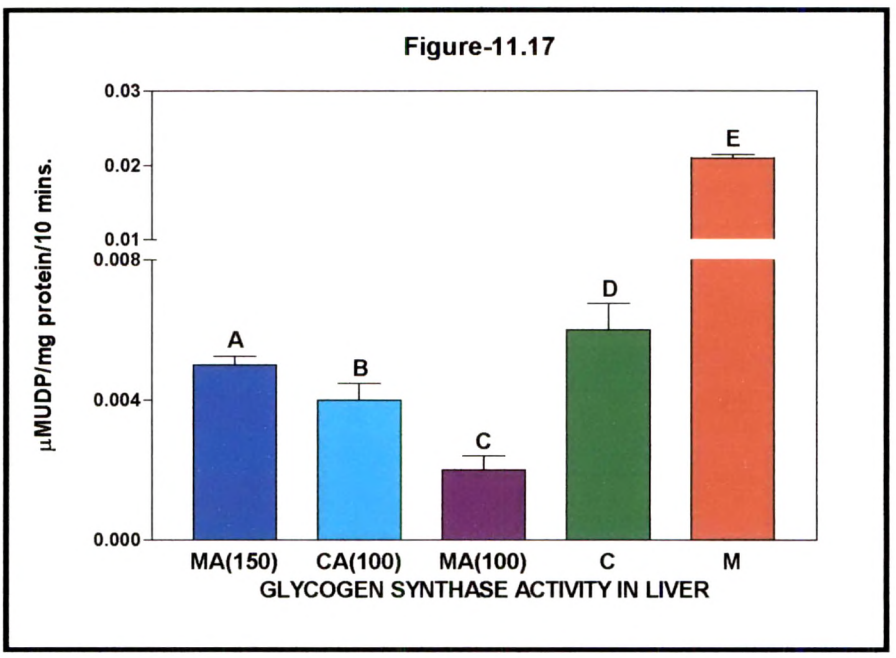


Table 11.17: Hepatic glycogen synthetase activity in adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
GLYCOGEN SYNTHETASE	0.005 ±0.00025	0.004 ±0.000475	0.002 ±0.000405	0.006 ±0.00075	0.021 ±0.000475

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	■	NS	◆	NS	NS	◆	◆	◆	◆

Values are expressed as mean ± SEM, ◆p<0.001; ■P<0.01;
NSNon Significant

Figure 11.19: Hepatic glycogen phosphorylase activity in adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

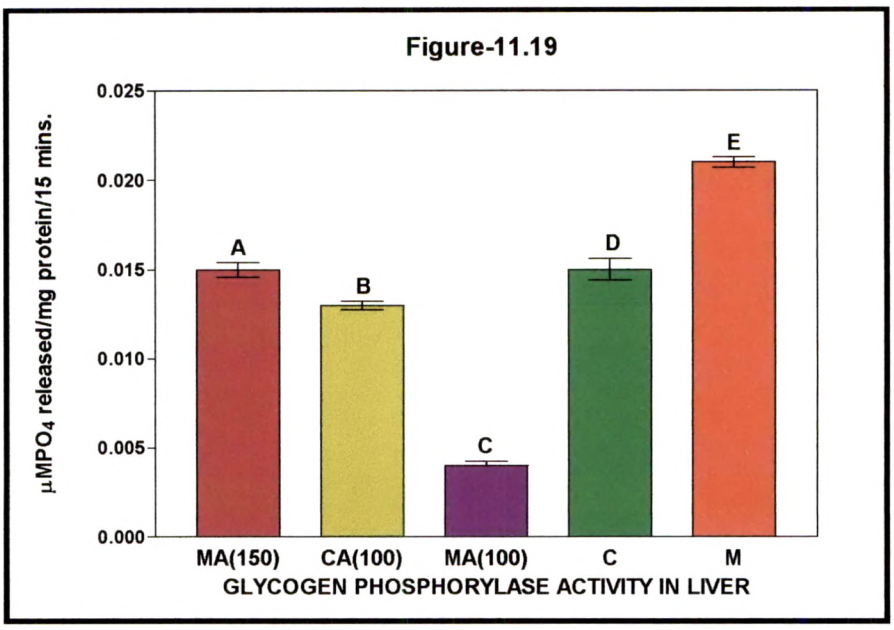


Table 11.19: Hepatic glycogen phosphorylase activity in adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
GLYCOGEN PHOSPHORYLASE	0.015 ±0.0004	0.013 ±0.00025	0.004 ±0.00025	0.015 ±0.0006	0.021 ±0.000285

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	●	◆	NS	◆	◆	●	◆	◆	◆	◆

Values are expressed as mean ± SEM, ◆p<0.001; ●P<0.05; NSNon Significant

Figure 11.20: Muscle glycogen phosphorylase activity in adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

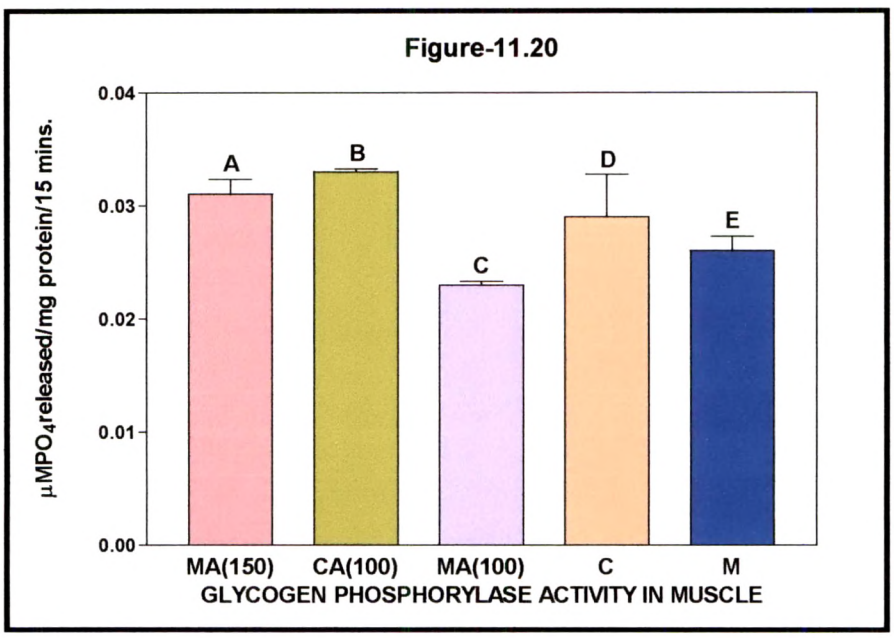


Table 11.20: Muscle glycogen phosphorylase activity in adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
GLYCOGEN PHOSPHORYLASE	0.031 ±0.00135	0.033 ±0.00025	0.023 ±0.000285	0.029 ±0.00375	0.026 ±0.00125

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	NS	NS	NS	•	NS	NS	NS	NS	NS

Values are expressed as mean ± SEM, •P<0.05; NSNon Significant

Figure 11.21: Hepatic glucose-6-phosphatase activity in adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

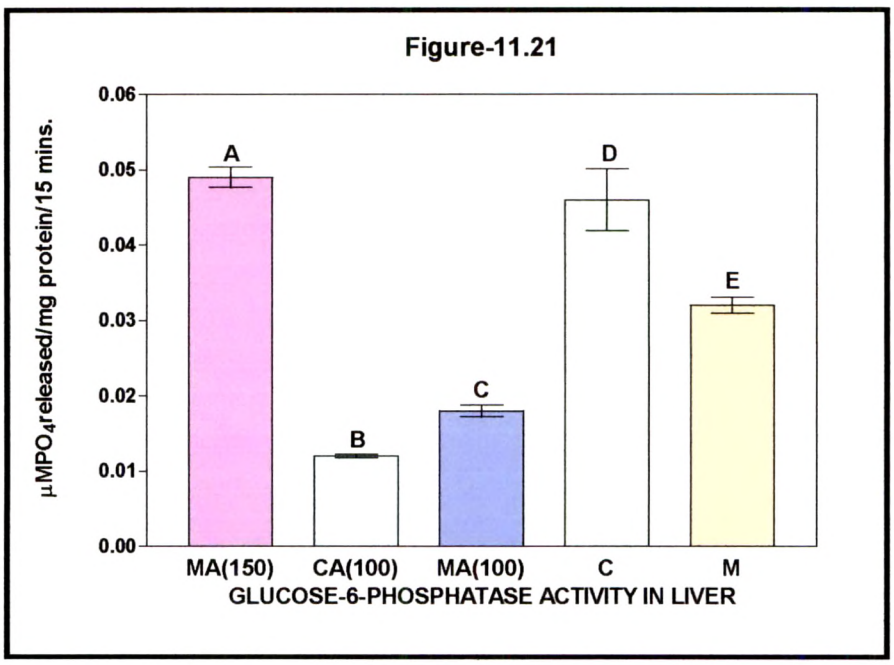


Table 11.21: Hepatic glucose-6-phosphatase activity in adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
GLUCOSE-6-PHOSPHATASE	0.049 ±0.00135	0.012 ±0.00025	0.018 ±0.0008	0.046 ±0.0041	0.032 ±0.00105

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	◆	◆	NS	◆	NS	◆	◆	◆	■	■

Values are expressed as mean ± SEM, ◆p<0.001; ■P<0.01; NSNon Significant

Figure 11.22: Hepatic protein content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

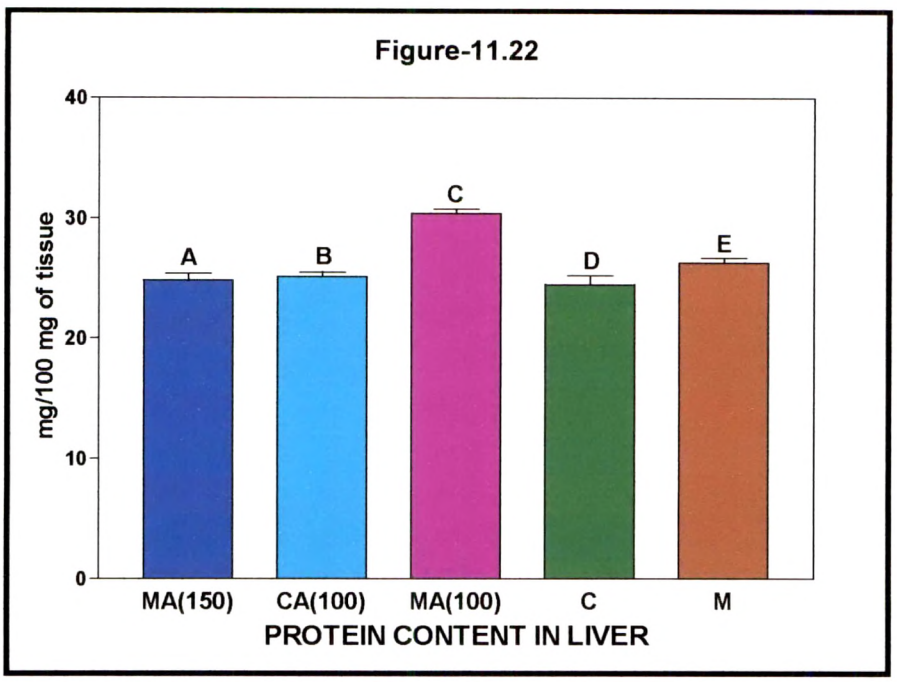


Table 11.22: Hepatic protein content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
PROTEIN	24.82 ±0.552	25.16 ±0.347	30.41 ±0.344	24.49 ±0.7485	26.32 ±0.408

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	◆	NS	NS	◆	NS	NS	◆	◆	NS

Values are expressed as mean ± SEM, ◆p<0.001; NSNon Significant

Figure 11.23: Muscle protein content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

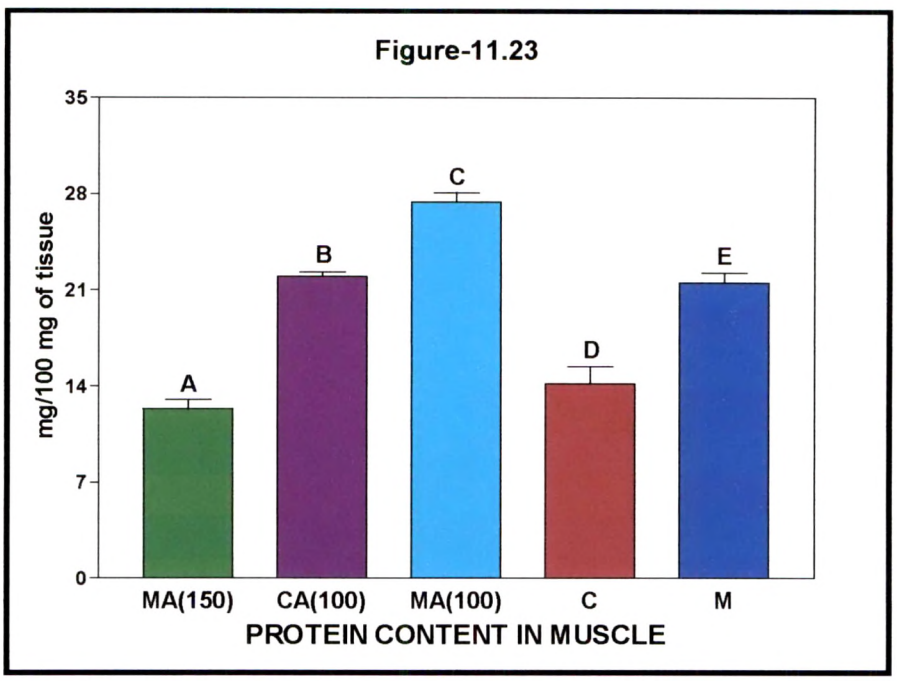


Table 11.23: Muscle protein content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
PROTEIN	12.33 ±0.694	21.99 ±0.303	27.41 ±0.685	14.16 ±1.2595	21.54 ±0.724

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	◆	◆	NS	◆	■	◆	NS	◆	■	◆

Values are expressed as mean ± SEM, ◆p<0.001; ■P<0.01; NSNon Significant

Figure 11.24: Hepatic total lipid content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

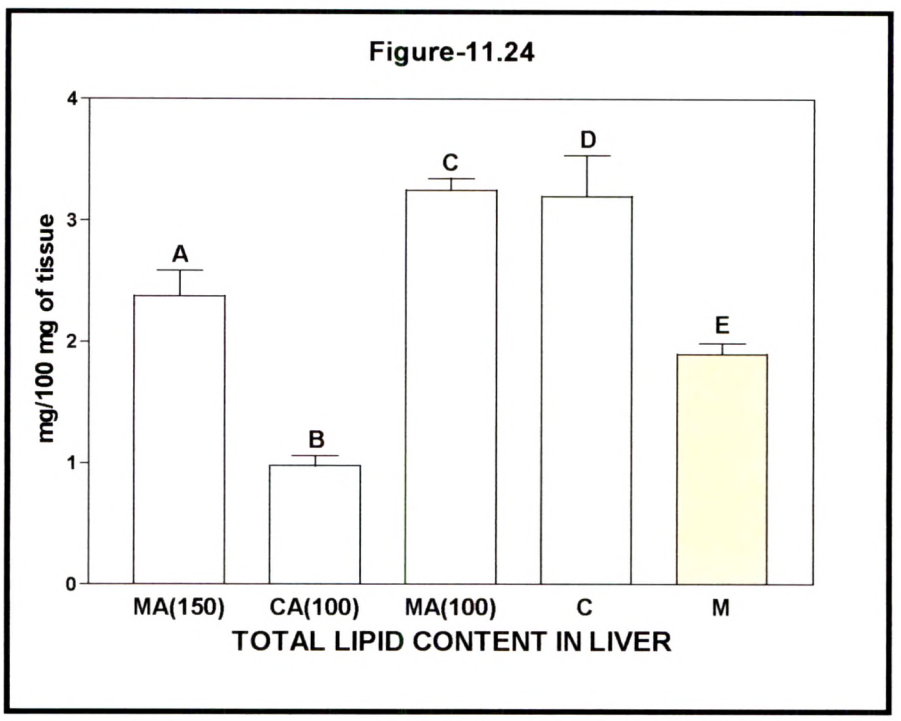


Table 11.24: Hepatic total lipid content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
TOTAL LIPIDS	2.375 ±0.2096	0.975 ±0.0853	3.25 ±0.0957	3.2 ±0.33415	1.9 ±0.0912

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	■	NS	NS	NS	◆	◆	●	NS	■	■

Values are expressed as mean ± SEM, ◆p<0.001; ■P<0.01; ●P<0.05; NSNon Significant

Figure 11.25: Hepatic cholesterol content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

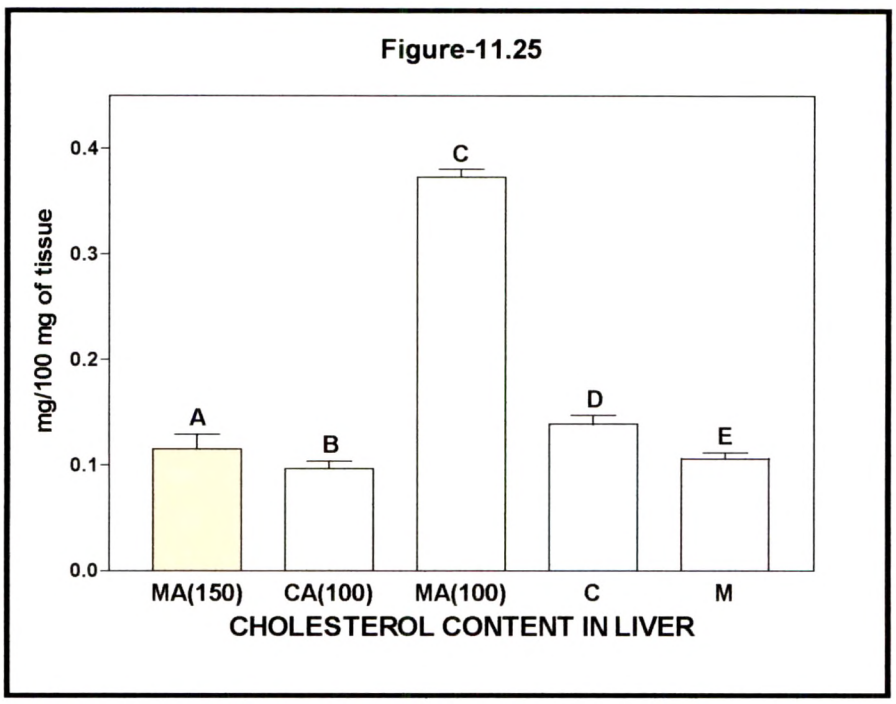


Table 11.25: Hepatic cholesterol content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
CHOLESTEROL	0.1156 ±0.015	0.0969 ±0.00685	0.3731 ±0.0073	0.1391 ±0.0084	0.1065 ±0.00565

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	◆	NS	NS	◆	NS	NS	◆	◆	NS

Values are expressed as mean ± SEM, ◆p<0.001; NSNon Significant

Figure 11.26: Muscle total lipid content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

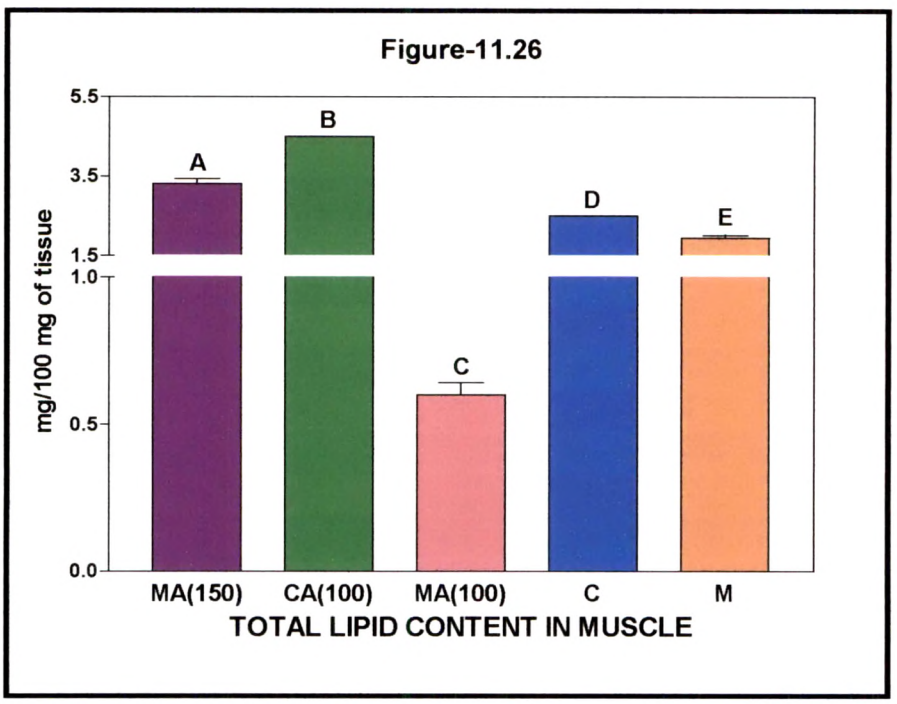


Table 11.26: Muscle total lipid content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
TOTAL LIPIDS	3.3 ±0.129	4.5 ±0.00006	0.6 ±0.0408	2.5 ±0.00006	1.95 ±0.0645

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆

Values are expressed as mean ± SEM, ◆p<0.001

Figure 11.27: Muscle cholesterol content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

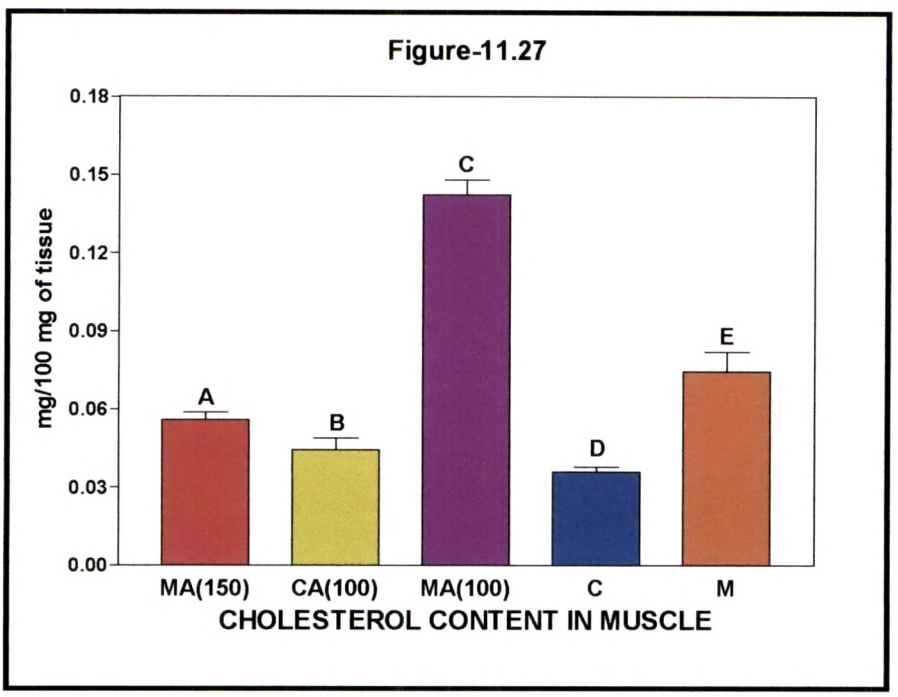


Table 11.27: Muscle cholesterol content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
CHOLESTEROL	0.0559 ±0.0028	0.0445 ±0.0045	0.1425 ±0.0056	0.036 ±0.0018	0.0745 ±0.0075

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	◆	NS	NS	◆	NS	■	◆	◆	◆

Values are expressed as mean ± SEM, ◆p<0.001; ■P<0.01;
NSNon Significant

Figure 11.28: Adipose tissue total lipid content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

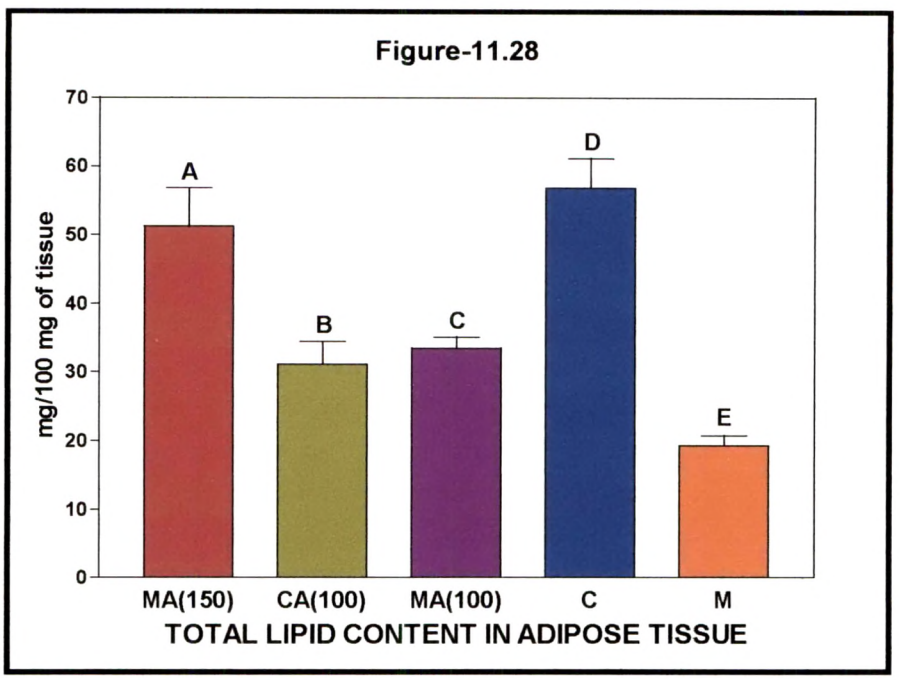


Table 11.28: Adipose tissue total lipid content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
TOTAL LIPIDS	51.25 ±5.5438	31.1 ±3.54	33.475 ±1.611	56.8 ±4.3395	19.275 ±1.4778

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	●	●	NS	◆	NS	■	NS	■	NS	◆

Values are expressed as mean ± SEM, ◆p<0.001; ■P<0.01; ●P<0.05; NSNon Significant

Figure 11.29: Adipose tissue cholesterol content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

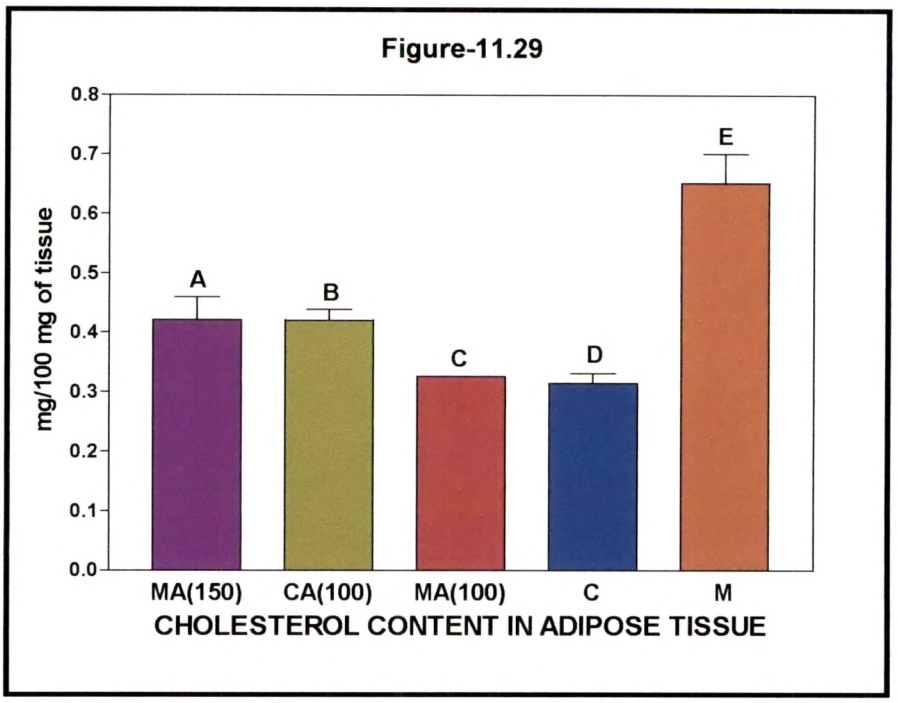


Table 11.29: Adipose tissue cholesterol content of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
CHOLESTEROL	0.421 ±0.0382	0.4205 ±0.0184	0.3262 ±0.00	0.3148 ±0.016	0.6514 ±0.05

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	NS	NS	◆	NS	NS	◆	NS	◆	◆

Values are expressed as mean ± SEM, ◆p<0.001; NSNon Significant

Figure 11.30: Serum triglyceride level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

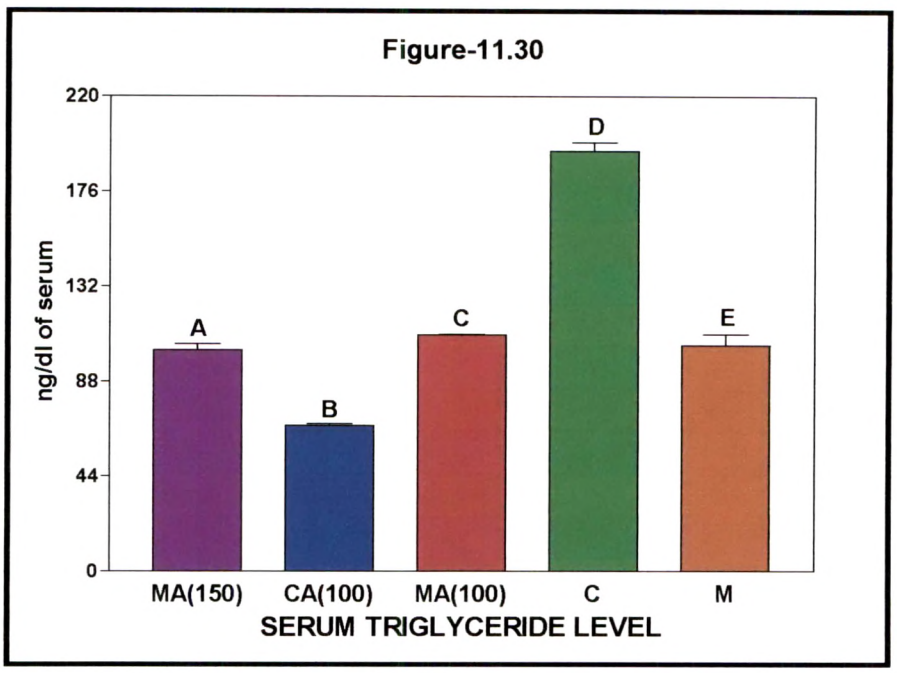


Table 11.30: Serum triglyceride level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
TRIGLYCERIDE	102.54 ±2.735	67.63 ±0.728	109.45 ±0.4131	194.94 ±3.8433	104.84 ±4.963

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	◆	NS	◆	NS	◆	◆	◆	◆	NS	◆

Values are expressed as mean ± SEM, ◆p<0.001; NSNon Significant

Figure 11.31: Serum cholesterol level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

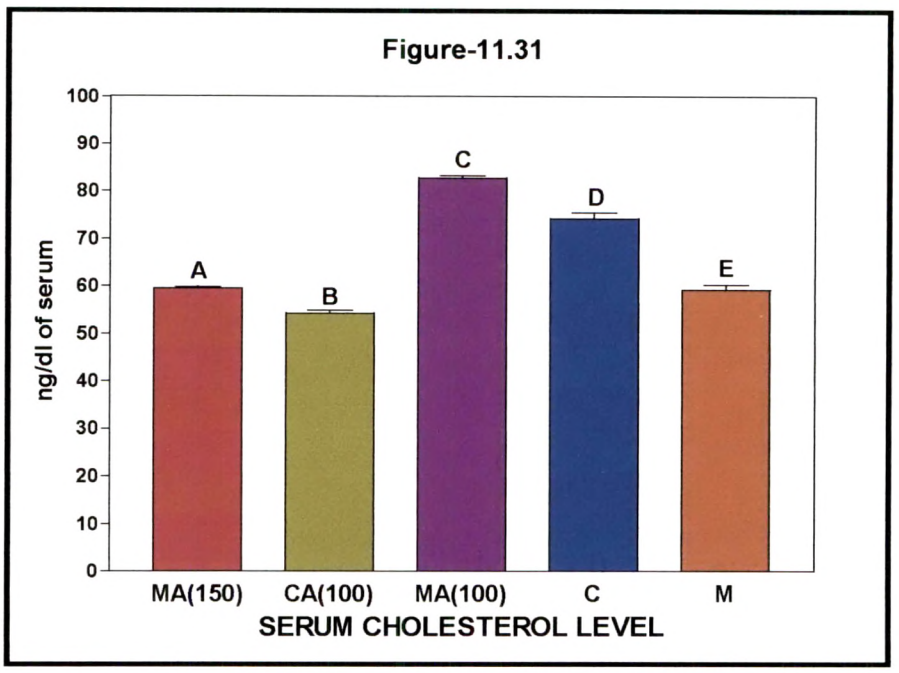


Table 11.31: Serum cholesterol level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
CHOLESTEROL	59.52 ±0.3014	59.29 ±0.556	82.81 ±0.4305	74.31 ±1.2021	59.25 ±1.0557

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	◆	◆	NS	◆	◆	NS	◆	◆	◆

Values are expressed as mean ± SEM, ◆p<0.001; NSNon Significant

Figure 11.32: Serum total lipid level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

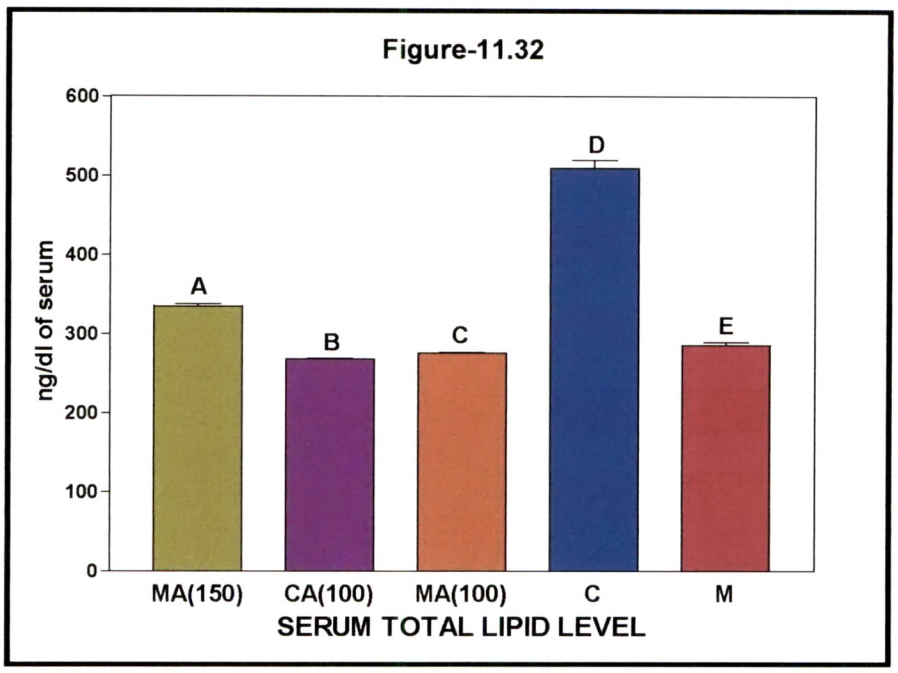


Table 11.32: Serum total lipid level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
TOTAL LIPIDS	334.95 ±2.394	267.66 ±1.2815	275.61 ±1.204	509.75 ±9.78	286.05 ±3.348

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	◆	◆	◆	◆	NS	◆	NS	◆	NS	◆

Values are expressed as mean ± SEM, ◆p<0.001; NSNon Significant

Figure 11.33: Serum phospholipid level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

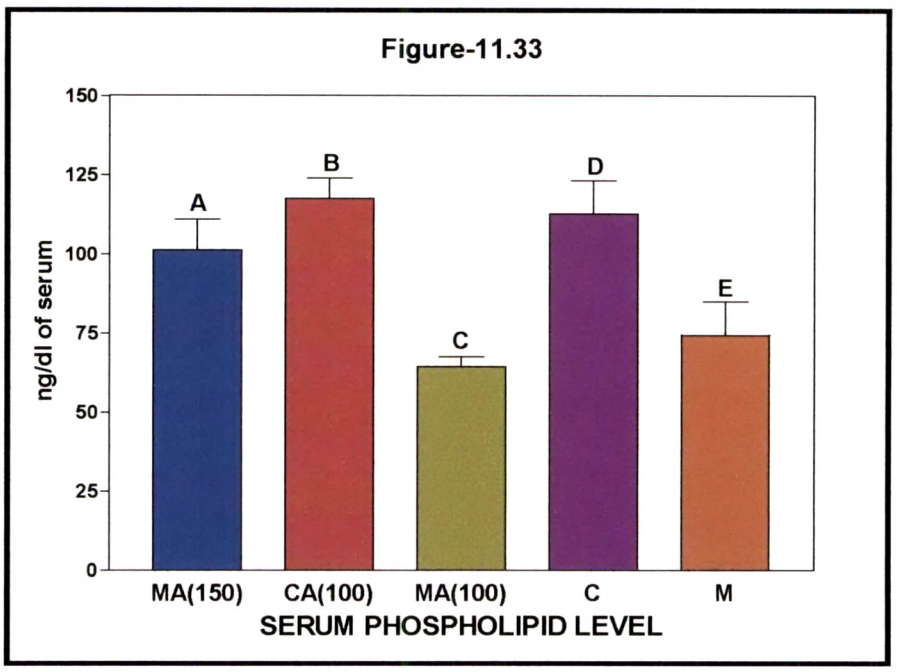


Table 11.33: Serum phospholipid level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
PHOSPHOLIPID	101.27 ±9.7489	117.62 ±6.265	64.55 ±2.9555	112.76 ±10.4413	74.47 ±10.44

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	NS	NS	NS	NS	■	NS	●	●	NS	NS

Values are expressed as mean ± SEM, ◆p<0.001; ▪P<0.01;
NSNon Significant

Figure 11.34: Serum free fatty acid level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

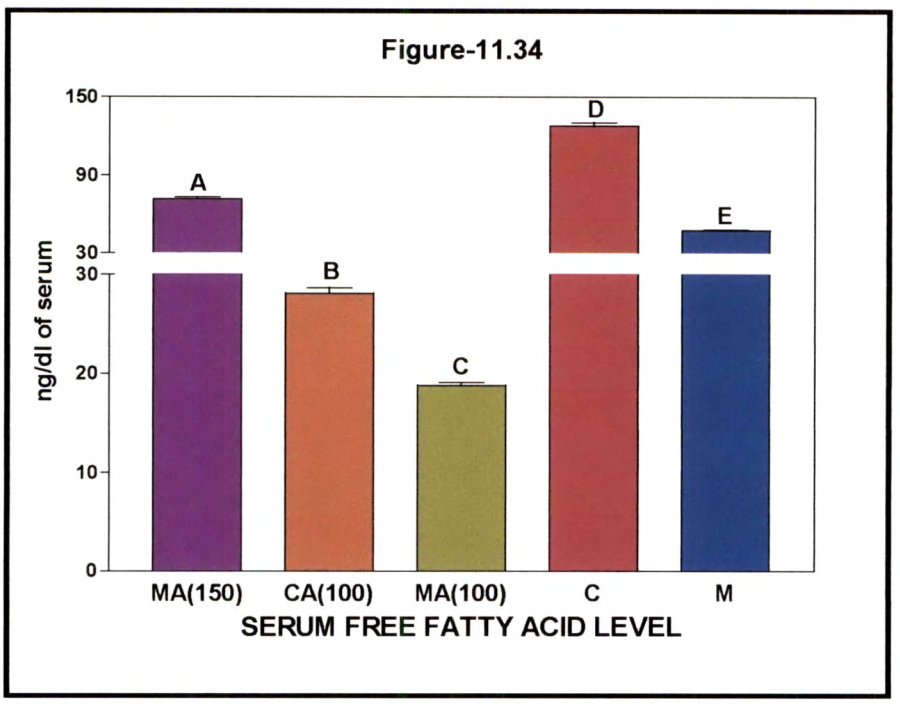


Table 11.34: Serum free fatty acid(FFA) level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)	CA(100)	MA(100)	C	M
SERUM FFA	71.62 ±1.26	28.12 ±0.54	18.8 ±0.31	127.74 ±2.65	47.49 ±0.64

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	◆	◆	◆	◆	■	◆	◆	◆	◆	◆

Values are expressed as mean ± SEM, ◆p<0.001; ■P<0.01

Figure11.35: Serum insulin level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

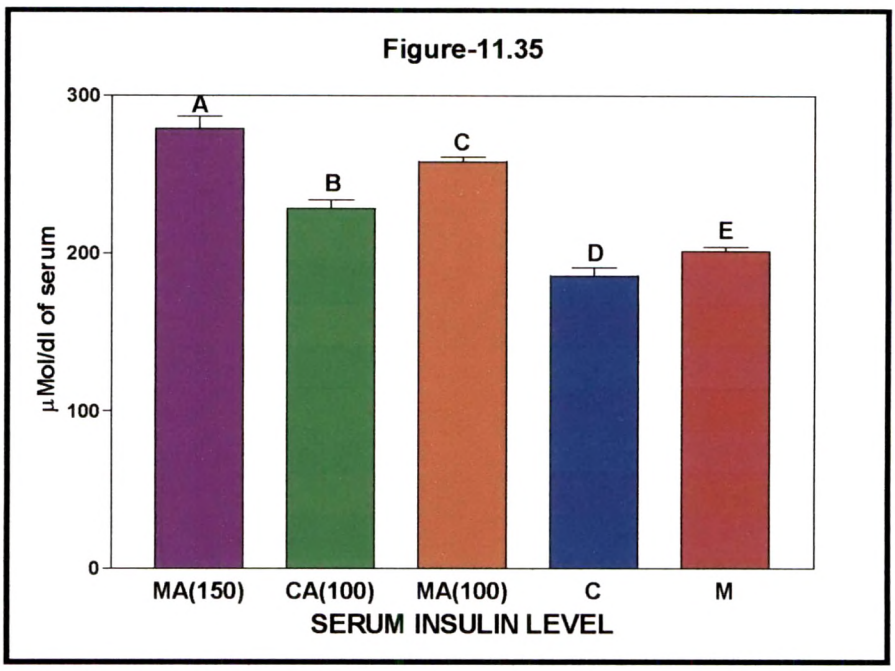


Table11.35: Serum insulin level of adult rats on 60th day subjected to neonatal melatonin treatment and weaning alloxanisation on 22nd day:

	MA(150)(A)	CA(100)(B)	MA(100)(C)	C(D)	M(E)
INSULIN	279.11 ±7.564	228.41 ±5.623	258.23 ±2.896	185.82 ±5.259	201.66 ±2.5995

Bonferroni's Multiple Comparison Test

	AvsB	AvsC	AvsD	AvsE	BvsC	BvsD	BvsE	CvsD	CvsE	DvsE
p	◆	NS	◆	◆	■	◆	●	◆	◆	NS

Values are expressed as mean ± SEM, ◆p<0.001; ■P<0.01; ●P<0.05; NSNon Significant

PLATE – 14

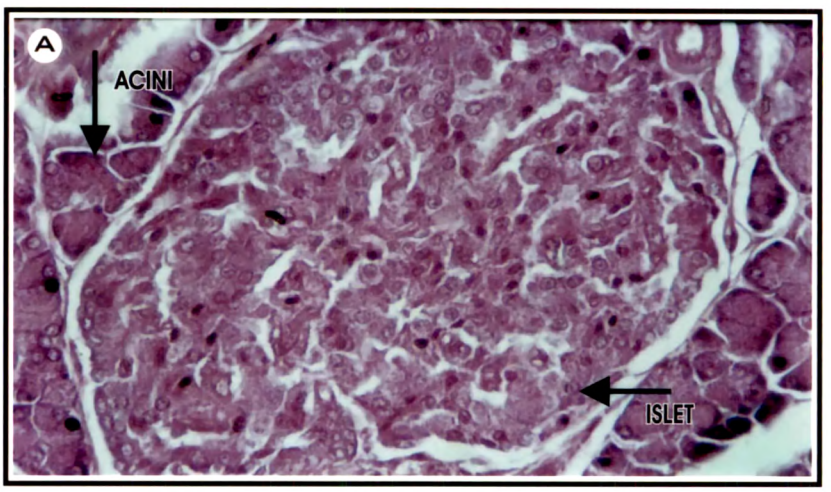
Photomicrographs of sections of pancreas – 450 X

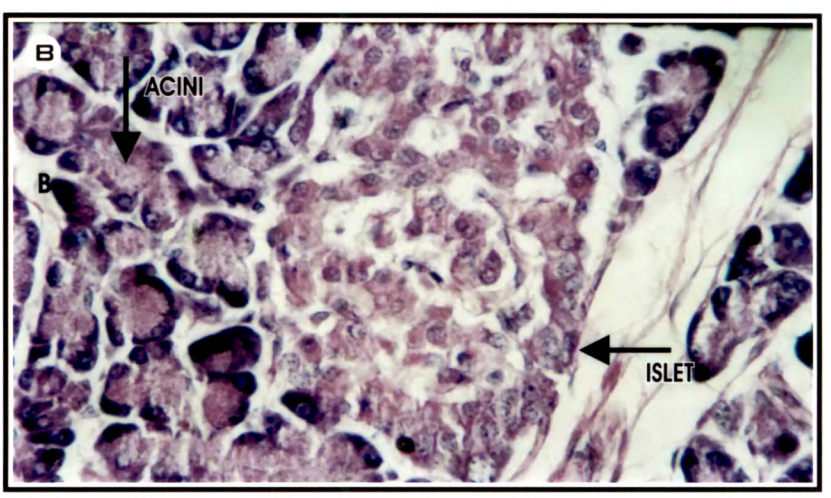
FIGURE (A): Transverse section of the pancreas of male hypermelatonemic alloxanised (100) rats on the 60th day showing islet and pancreatic acini. The islet and acinar cells are compactly packed with increased number of B and A cells.

FIGURE (B): Transverse section of the pancreas of male control alloxanised (100) adult (60th day) rats showing islet and pancreatic acini. The islet cells are loosely packed with a reduced B:A cells ratio. Large clear areas can be marked off due to the damage caused by alloxan in the islet and acinar areas.

FIGURE (C): Transverse section of the pancreas of male hypermelatonemic alloxanised (150) rats on the 60th day showing islet and pancreatic acini. The islet size is increased as well as the B:A cells ratio is increased.

PLATE - 14





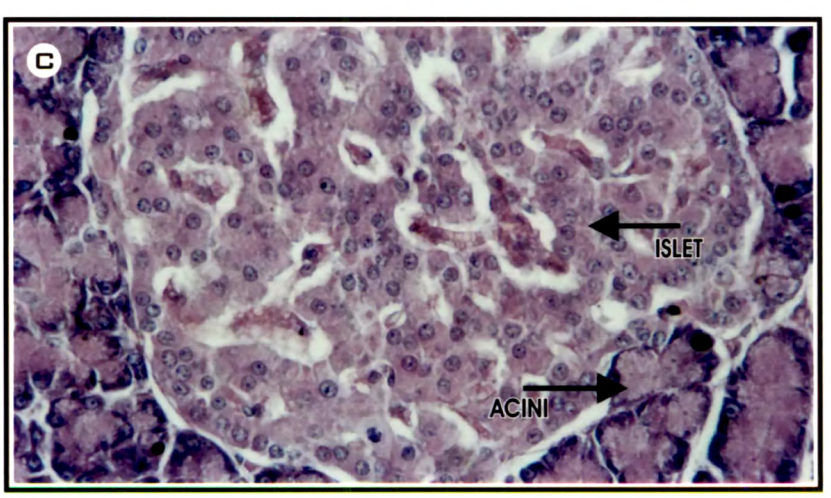


PLATE – 15

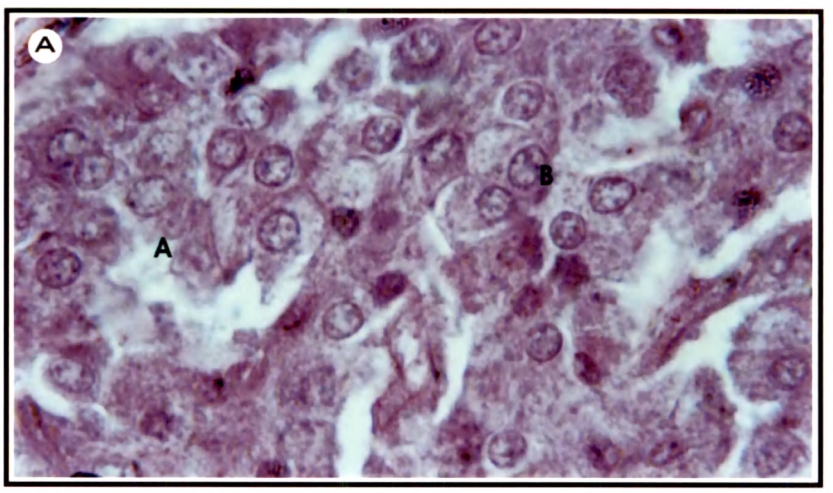
Photomicrographs of sections of pancreas – 1000 X

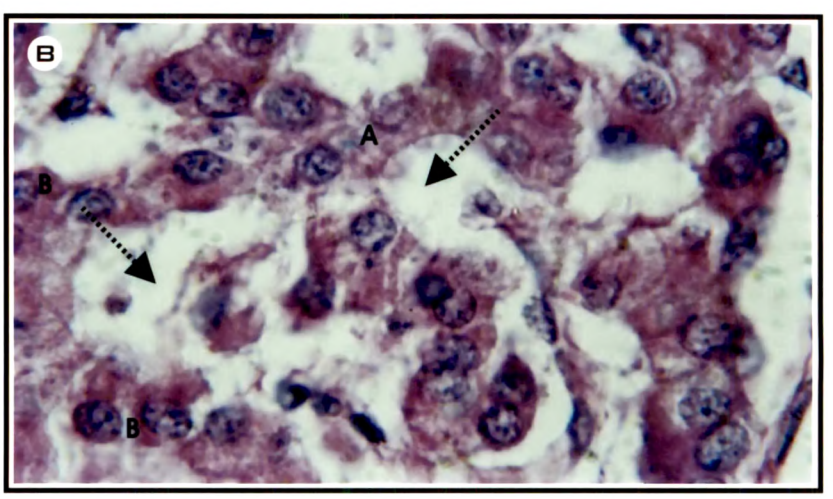
FIGURE (A): Transverse section of the pancreas of male hypermelatonemic alloxanised (100) rats on the 60th day showing islet and pancreatic acini The islet and acinar cells are compactly packed with increased number of B and A cells.

FIGURE (B): Transverse section of the pancreas of male control alloxanised (100) adult (60th day) rats showing islet and pancreatic acini The islet cells are loosely packed with a reduced B A cells ratio. Large clear areas (dotted arrows) can be marked off due to the damage caused by alloxan in the islet and acinar areas.

FIGURE (C): Transverse section of the pancreas of male hypermelatonemic alloxanised (150) rats on the 60th day showing islet and pancreatic acini The islet size is increased as well as the B:A cells ratio is increased.

PLATE - 15





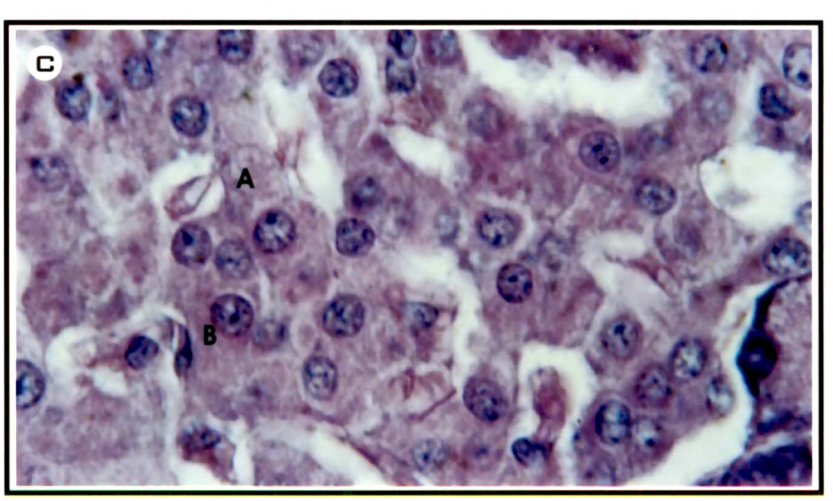


PLATE – 16

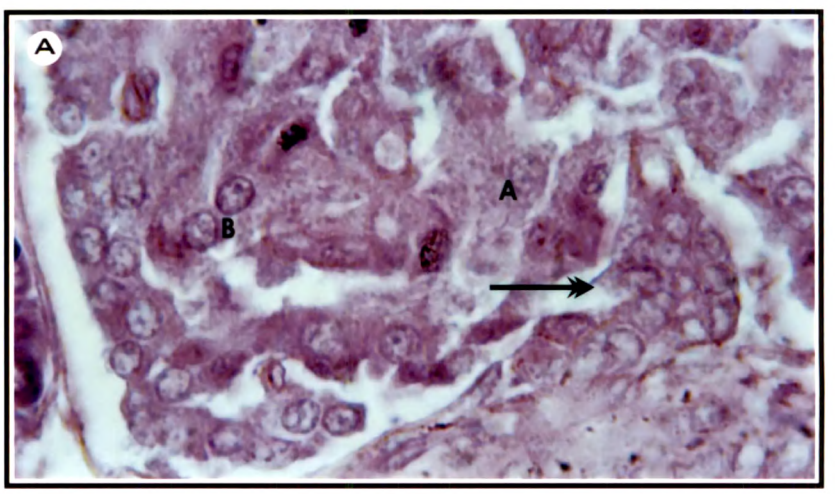
Photomicrographs of sections of pancreas – 1000 X

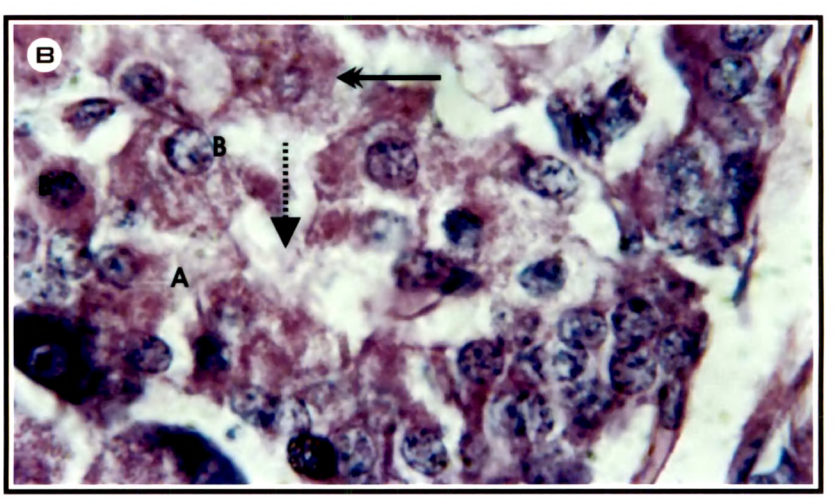
FIGURE (A): Transverse section of the pancreas of male hypermelatonemic alloxanised (100) rats on the 60th day showing islet and pancreatic acini. The islet and acinar cells are compactly packed with increased number of B and A cells. Note the transdifferentiation of acinar cells into the islet cells.

FIGURE (B): Transverse section of the pancreas of male control alloxanised (100) adult (60th day) rats showing islet and pancreatic acini The islet cells are loosely packed with a reduced B.A cells ratio. Large clear areas (dotted arrows) can be marked off due to the damage caused by alloxan in the islet and acinar areas. Some transdifferentiation of acinar cells into cells is also visible although to a lesser extent as compared to the treatment sections.

FIGURE (C): Transverse section of the pancreas of male hypermelatonemic alloxanised (150) rats on the 60th day showing islet and pancreatic acini. The islet size is increased as well as the B:A cells ratio is increased. The hypertrophy of the B cells is well marked by the darkly stained cells in the section.

PLATE - 16





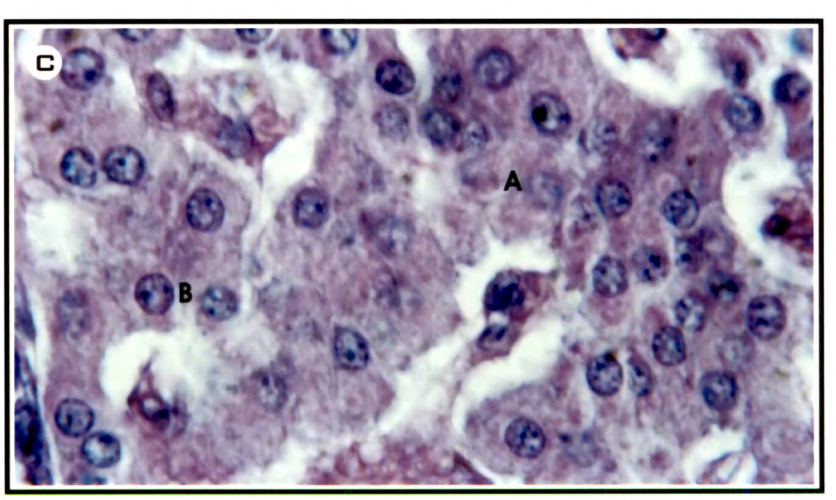


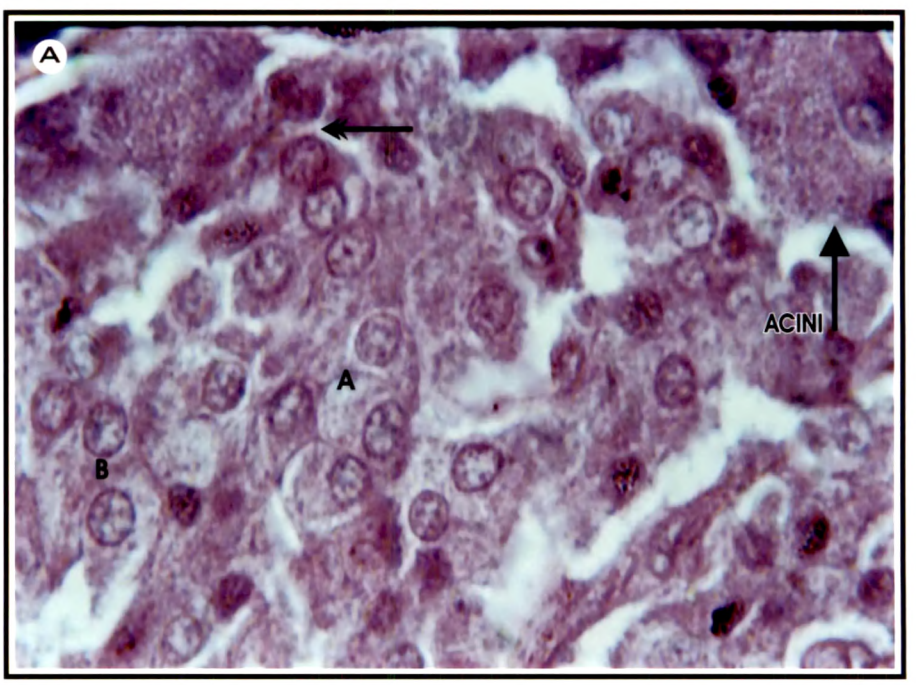
PLATE – 17

Photomicrographs of sections of pancreas – 1000 X

FIGURE (A): Transverse section of the pancreas of male hypermelatonemic alloxanised (100) adult (60^{th} day) rats showing islet and pancreatic acini. Note the transdifferentiation (double headed arrow) of the acinar cells into the islet cells.

FIGURE (B): Transverse section of the pancreas of male hypermelatonemic alloxanised (100) rats on the 60^{th} day showing islet and pancreatic acini. Note the transdifferentiation (double headed arrow) of the acinar cells into the islet cells. The B:A cell ratio is increased with a prominent hypertrophy of the B cell by neogenesis by transdifferentiation,

PLATE - 17



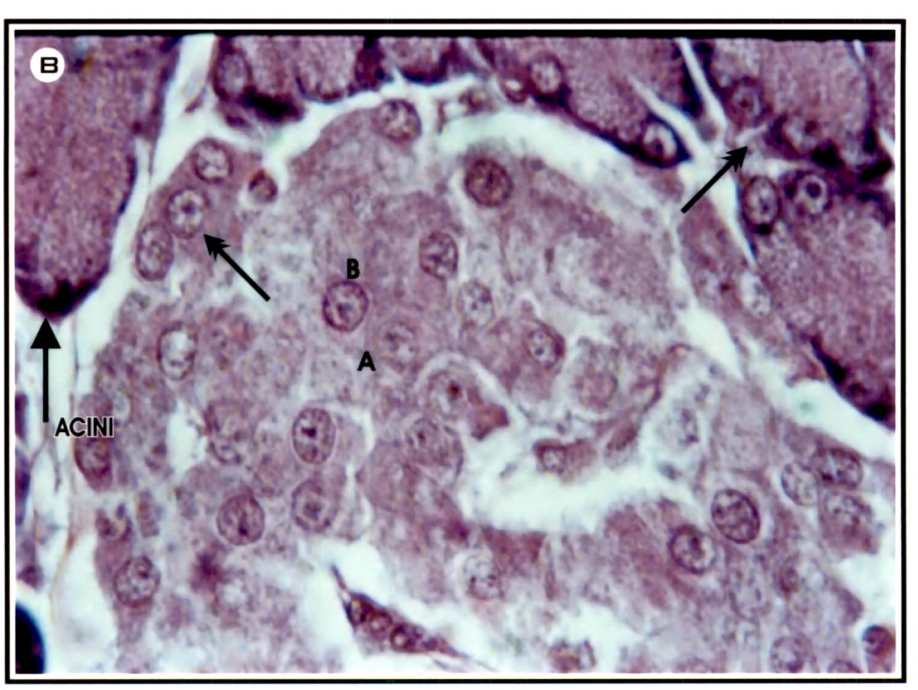


PLATE – 18

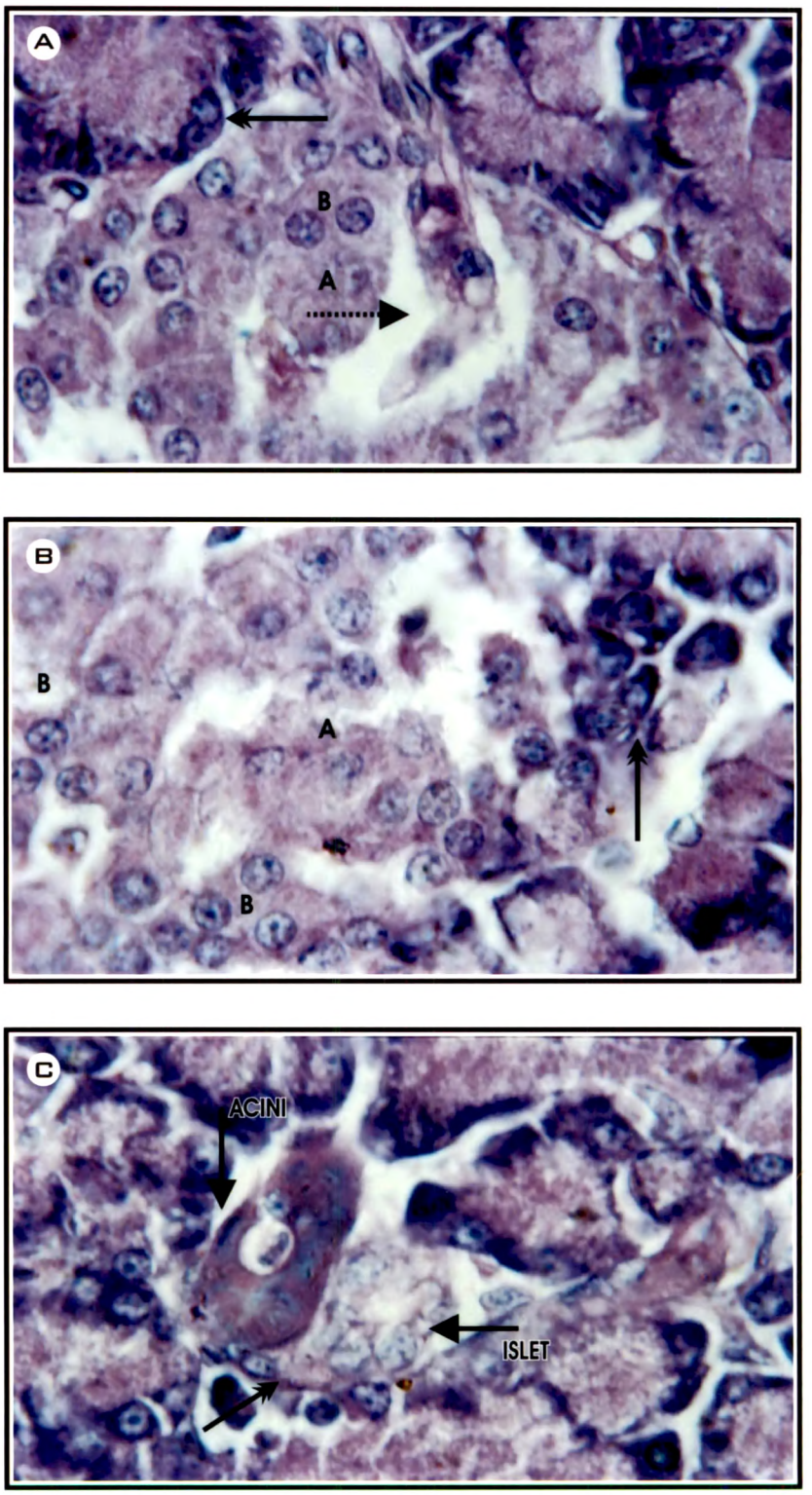
Photomicrographs of sections of pancreas – 1000 X

FIGURE (A): Transverse section of the pancreas of male hypermelatonemic alloxanised (150) rats on the 60th day showing islet and pancreatic acini. The islet and acinar cells are loosely packed marked by clear areas (dotted arrow) in the section with, increased number of B and A cells. The hypertrophy of B cells is well marked by the transdifferentiation (double headed arrow) of the acinar cells into the islet cells.

FIGURE (B): Transverse section of the pancreas of male hypermelatonemic alloxanised (150) adult (60th day) rats showing islet and pancreatic acini. The islet cells are loosely packed with a reduced B:A cells ratio. Note the transdifferentiation of the acinar cells into the islet cells.

FIGURE (C): Transverse section of the pancreas of male hypermelatonemic alloxanised (150) rats on the 60th day showing islet and pancreatic acini.

PLATE - 18



Histological observations: The islets show pronounced recovery from alloxan induced damage Islets of both alloxan treated control and nMT rats show prominent cells with a higher B:A cell ratio. Fully, differentiated and still transforming cells can be seen in both islets. Sections clearly show transdifferentiation of acinar to B cell at the interjunction between islet and acinar tissue (Plate; 14-18).

DISCUSSION:

The results obtained in the present study suggest significant changes with respect to metabolic features as well as histoarchitecture of pancreatic islets due to weaning alloxan challenge in both nMT as well as non nMT rats with more remarkable effects on nMT rats as long term effects Both nMT as well as non nMT rats show significant differential alteration in body and organ weights as young adults due to weaning alloxan treatment. Whereas, the non nMT rats show a 22% decrement in body weight the nMT rats show a dose dependent increment (5% in 100 mg and 27% in 150 mg alloxan) compared to age matched non alloxanised rats (Fig. and Tab , 11.1. This increase in body weight might be related with the dose dependent (alloxan) increase in body lipid content recorded in nMT rats. This increase in body lipid load is also seen in non nMT rats The increase in body lipid content is marked by a reciprocal decrement in serum lipid fractions (Fig. and Tab.; 11.31-11 34). Since the nMT rats show relatively higher serum lipid profiles as well as tissue lipid loads, it is likely that a progressive insulin resistance is setting in these rats as a consequence of neonatal melatonin treatment and long term effect of weaning

alloxan treatment It would be worth investigating about the consequential effect of neonatal hypermelatonemia on the proneness to develop insulin resistance in NIDDM. Development of obesity with increased tissue triglyceride content with concomitant hyperinsulinemia and insulin resistance has been reviewed by Koyama *et al*, (1997). In the present study on weaning alloxan treatment seems to suggest development of insulin resistance and hyperinsulinemia as long term effects probably more potentiated by a higher melatonin level in the neonatal period (Fig and Tab ; 11.35). This is in contrast to early neonatal (1^{st} week) streptozotocin or alloxan induced diabetes where hyperglycemia and hyperlipidemia have been projected as long term effects but with a hypoinsulinemic status. The hyperinsulinemia seen in the present study together with increased tissue and serum lipid contents and similar to the reported hyperglycemia, hyperinsulinemia and hyperlipidemia together with increased tissue lipid content in adult rats born to mother subjected to streptozotocin induced diabetes during the gestation period (Merzouk *et al.*, 2000). The above inferred insulin resistance in the context of increased tissue lipid content and hyperlipidemia is substantiated by the depletion in significant hepatic and muscle glycogen content with hyperglycemia in alloxan treated non nMT as well as non nMT rats, more pronounced in the latter. A protein anabolic influence related to insulin resistance is also evident as the tissue protein contents are significantly increased in nMT rats (Fig. and Tab.; 11.22, 11 23). The purported insulin resistance in nMT rats could also be due to increased corticosterone action and the relative weights

of adrenals is increased in nMT rats. The deleterious effect of alloxan in nMT rats is emphasized by the significant dose dependent decrease in the relative weight of kidneys and spleen (Fig. and Tab.; 11 10, 11.11) Interestingly the low dose of alloxan increases the relative weight of pancreas, the higher dose decreases like in the non nMT rats (Fig and Tab.; 11.8). This could be related with the more healthy B cells in the islets of low dose alloxan treated rats as against more B cell damage in the high dose Protective action of neonatal melatonin o alloxan induced B cell damage is clearly seen from the histologically observable structural features of pancreatic islets (Plate; 14-18). Though the higher dose of alloxan thus induces a relatively greater B cell damage prior melatonin treatment seems to potentiate the regenerative ability especially by promoting acinar cell transdifferentiation. Though other worker have shown islet cell regeneration and transdifferentiation of acinar cell under hyperglycemic or hyperinsulinemic stress (see Sjoholm, 1996; Fernandez *et al.*, 1997; Bonner Weir, 2000; Lipsett and Finegood, 2002; Paris *et al.*, 2003; Arulmozhi *et al.*, 2004), this is the only study which has shown the ability of pretreatment of melatonin in B cell regeneration and transdifferentiation from acinar cells when subjected to alloxan insult in the weaning age (Plate; 14-18)

In conclusion it can be said that neonatal melatonin treatment has favorable influence on B cell survival and regeneration under alloxan insult However, as a long term effect of weaning alloxan induced diabetes, neonatal melatonin treatment tends to potentiate

hyperinsulinemia and insulin resistance and thereby predispose these animals to NIDDM.

SUMMARY:

A favorable influence of nMT on insulin sensitivity and insulin induced oxidation potential has been noted and hence it was thought pertinent to study the influence of nMT on long term effects on histological features of pancreas and carbohydrate, lipid and protein metabolic profiles of adult rats in relation to alloxan administration at the weaning age (22^{nd} day). To this end rat neonates have been treated with melatonin in graded doses of 200 µg/animal from day 1 to day 7; 400 µg/animal from day 8 to day 14 and 600 µg/animal from day 15 to day 21 to generate neonatal hypermelatonemic status; a low (100 µg/kg) dose and a high dose (150 µg/kg) of alloxan were given on the 22^{nd} day and assessed on the 60^{th} day The body weight of MA(150) rats increased significantly as compared to CA(100) and MA(100) rats while, the body weights of CA(100) and MA(100) rats decreased significantly as compared to the C rats and that of MA(150) remained unaltered. In the MA(100) rats, the relative weight of pancreas, liver kidney and adrenal increased significantly as compared to MA(150) and CA(100) and C rats. There is a significant increase in the relative weight of spleen and testes of CA(100) rats as compared to MA(150) and MA(100) rats The hepatic and muscle glycogen content decreased significantly in the all the alloxanised groups as compared to the age matched control and nMT rats. The serum insulin and glucose

levels increased significantly in all the alloxanised rats as compared to the controls of the same age. The activity of hepatic and muscle glycogen synthetase decreased significantly in all the alloxanised groups as compared to nMT rats of the same age. The hepatic glycogen phosphorylase activity decreased significantly in the MA(100) rats as compared to all the other groups. The hepatic glucose-6-phosphatase activity decreased significantly in the CA(100) and MA(100) rats as compared to MA(150) and control rats of the same age. The muscle protein content of the MA(100) rats increased significantly as compared to all other groups). The hepatic total lipid content of the CA(100) rats decreased significantly as compared to all other groups while, the hepatic cholesterol content of MA(100) rats increased significantly as compared to all other groups. The muscle total lipid content of the MA(100) rats decreased significantly as compared to all other groups while, the muscle cholesterol content of MA(100) rats increased significantly as compared to all other groups. The total lipid content of CA(100) and MA(100) rats decreased significantly as compared to both MA(150) and controls of the same age but were significantly increased as compared to the age matched nMT rats. The adipose tissue cholesterol content of MA(150), CA(100), MA(100) and control rats decreased significantly as compared to the age matched nMT rats. The serum triglyceride level of all the groups decreased significantly as compared to the control rats of the same age. The serum cholesterol level of MA(100) rats increased significantly as compared to all other groups of the same

age. The serum total lipid level of all the groups decreased significantly as compared to control rats of the same age. The serum phospholipid level of MA(100) rats decreased significantly as compared to the MA(150), CA(100) and control rats of the same age. The serum free fatty acid level of MA(100) rats decreased significantly as compared to all the treatment and control groups of the same age The islets showed pronounced recovery from alloxan induced damage. Islets of both alloxan treated control and nMT rats showed prominent cells with a higher B:A cell ratio. Sections clearly showed transdifferentiation of acinar cells to B cells at the interjunction between islet and acinar tissue. It can be concluded from the above observations that neonatal melatonin treatment has favorable influence on B cell survival and regeneration under alloxan insult. However, as a long term effect of weaning alloxan induced diabetes, neonatal melatonin treatment tends to potentiate hyperinsulinemia and insulin resistance and thereby predispose these animals to NIDDM.