The first important experimental contribution in diabetes research was made by Bernard who discovered the production of glucose and formation of glycogen by the liver. Bernard also showed that puncture of the floor of the fourth ventricle in the dog and rabbit provokes transient hyperglycemia and glycosuria - transient diabetes. Bernard focused attention on the liver and central nervous system in the etiology of diabetes mellitus and formulated the hypothesis of overproduction of sugar by the liver as a cause of diabetes mellitus (Bernard, 1877).

The chemical detection of sugar in the blood and urine which substituted its detection by tasting the urine was described by Trommer in 1841 and Fehling in 1848 (as quoted by Papaspyros, 1964). The detection of acetone in diabetics was first described by Petter in 1857 and Gerhardt in 1865 (as quoted by Papaspyros, 1964) described a method for detecting ketone bodies in the urine and blood. These classical biochemical tests opened vistas in the objective study of experimental and spontaneous diabetes. The second important experimental step in the study of diabetes was the production of permanent diabetes mellitus by total pancreatectomy in dogs (von Mering and Minkowski, 1889 and Minkowski, 1892).

This experimental post-pancreatectomy diabetes was not only permanent but also showed most of the symptoms of severe spontaneous human diabetes; hyperglycemia, glucosuria, polydipsia and polyuria. The polyphagia followed by loss of appetite and loss of body weight leading to
cochexia which is accompanied by ketonemia, ketonuria, acidosis, coma and death. It is interesting to note that polydipsia and polyuria were described by Brunner (1653-1727) (as quoted by Rudolf Korec, 1967) in his experiments "Experimenta nova circa pancreas" wherein he removed the pancreas of dogs and probably first produced experimental diabetes though unknowingly. Later it was shown that complete pancreatectomy provokes diabetes mellitus in every species. The discovery of von Mering and Minkowski (1889) stimulated the investigation of the function of pancreatic "Zellhaufen" discovered by Langerhans (1869). After ligature of pancreatic duct performed by Ssobolew (1900, 1902) the exocrine part of the pancreas degenerated and islets of Langerhans persisted and diabetes mellitus did not appear. Mc Callum (1909) showed that the removal this atropic pancreas with persisting islets cause diabetes and this observation cleared all the uncertainties between the relationship of islets of Langerhans and diabetes mellitus. This finding was later corroborated by the post-mortem observations in diabetic patients in which small, pathological or absent islets of Langerhans have been demonstrated (Lazarus and Volk, 1962).

Since the beginning of this century a search for active principle of Langerhans islets began. Although Ssobolew and his co-workers were not far from preparing an effective extract from whole pancreas or from pancreas with degenerated exocrine part, the first to succeed in preparing a parenterally effective extract lowering blood sugar in diabetic and normal dogs and later also in diabetic man were Banting and Best (1921).
The discovery of insulin by Banting and Best not only proved that the real cause of post-pancreatectomy diabetes is the elimination of islets of Langerhans but simultaneously - which is not frequent in discoveries - provided an effective - until now unsurpassed - therapeutic principle for diabetes mellitus. Simultaneous with these developments work on the interplay of other hormones in the genesis of diabetes mellitus was also progressing. In 1886, Marie described the association of diabetes with acromegaly and one year later Minkowski (1887) showed the association of acromegaly with eosinophilic adenoma of adenohypophysis. John's et al. (1927) produced hyperglycemia for the first time in dogs by injecting them with extracts of adenohypophysis. However the importance of this gland in experimental diabetes was elucidated by the classical work of Houssay and his school.

Houssay and Biasotti (1930a) showed that removal of hypophysis ameliorated considerably the post-pancreatectomy diabetes in toads and dogs. Houssay and Biasotti (1930b) and Houssay et al. (1932) further demonstrated the diabetogenic effect of extract of adenohypophysis in normal rats and normal, hypophysectomized, pancreatectomized dogs: These extracts caused hyperglycemia, glycosuria, ketonuria, hyperlipemia and hypercholesterolemia and increase the resistance to insulin and aggravated diabetes after partial and complete pancreatectomy. These effects were attributed to the presence of growth hormone, prolactin and adreno cortico trophic hormone (ACTH) in adenohypophyseal extracts. In 1937, Young proved that adenohypophyseal extracts have also pancreatic action and succeeded experimental metahypophyseal diabetes mellitus by repeated injections of large doses of anterior pituitary extracts.
In the rat no permanent meta-hypophyseal diabetes could be produced but in the dogs these extracts caused serious damage to the β-cells of the islets of Langerhans. A clinical analogue of experimental, metahypophyseal diabetes is the mild but often insulin resistant diabetes in acromegaly caused by the over production of growth hormone by the acidophil cells of the anterior pituitary. Long and Lukens (1936) showed that adrenalectomy ameliorates diabetes of pancreatectomized cats and Ingle (1941) produced a new type of temporary experimental diabetes in rats by the administration of large doses of glucocorticoid hormone - cortisone - and called it as steroid diabetes.

Apart from post-pancreatectomy diabetes the most important type of the experimental diabetes is produced by the parenteral administration of alloxan, the hyperglycemic - hypoglycemic effect of which was noted by Jacobs (1937) and permanent diabetogenic effect by Dunn Shaw and Mc Letchie (1943). The advantages of alloxan diabetes over other types of experimental diabetes should be mentioned in this context.

1. Alloxan selectively destroys β cells and so produces a diabetes very similar to spontaneous diabetes mellitus in man.

2. Alloxan is capable of producing diabetes in every species when appropriate doses and procedures are used.

3. The production of diabetes by alloxan obviates many difficulties of pancreatectomy especially in animals with a diffuse type of pancreas.
4. The severity of diabetes can be graded by the administration of graded doses of alloxan.

Recently many substances were discovered which interfere with some indispensable step(s) of the enzymatic degradation of glucose and some of them may also cause damage to the enzyme producing structure. The metabolic inhibitor type of experimental diabetes is produced by the administration of non-metabolizable glucose analogues such as 2-deoxy-D-glucose, 6-fluoroglucose, gold-thioglucose or by inhibitors of some steps of tricarboxylic acid cycle, eg. fluoroacetate (Wick et al., 1955; Brecker and Waxler, 1949 and Cole et al., 1955).

Streptozotocin (STZ)

Another diabetogenic compound which is gaining popularity recently is streptozotocin.

Like alloxan, streptozotocin is a relatively selective β cytotoxin in certain animal species, causing an initial triphasic glucose response and then permanent diabetes. Streptozotocin, an N-nitroso derivative of D-glucosamine, was initially isolated from cultures of streptomyces achromogenes, but subsequently has been synthesized in the laboratory (Herr et al., 1960). Cell membrane binding is again the likely first step in the pathologic process.

In the case of streptozotocin, the alpha monomer of the glucosamine moiety has been shown to render the compound more cytotoxic than the β monomer, suggesting that the drug's toxicity is mediated through specific
recognition by some receptor on the β cell (Rossini et al., 1977). It has further been suggested that the glucose component of streptozotocin enhances its uptake into the β cell where the cytotoxicity of the nitrosourea moiety can be concentrated (Schein and Loftus, 1968; Wilander and Gunnarson, 1975 and Gunnarson et al., 1974). Removal of the glucose moiety renders the compound much less specifically toxic for β cells (Dulin and Soret, 1977); substitution of galactose for glucose also decreases its effectiveness (Fischer and Rickert, 1975); within the β cells STZ is believed to reduce levels of nicotine adenine dinucleotide (NAD) by both decreasing its synthesis and increasing its breakdown (Gunnarson et al., 1974). Nicotinamide protects animals against the cytotoxicity of both STZ and alloxan. Histopathologically, β cell necrosis without insulitis is routinely observed (Dulin and Soret, 1977 and Ganda et al., 1976). As is the case with alloxan, certain carbohydrates have the ability to protect the β cell against streptozotocin, but among them only 3-O methyl glucose protects equally well against both (Ganda et al., 1976).

There is no doubt that no one type of experimental diabetes is completely identical with spontaneous human diabetes mellitus. However for want of better animal models most of the experimental works have been carried out in either alloxan diabetic or streptozotocin diabetic rats.

Research in diabetes mellitus is one of the top priority areas in medical research throughout the world and huge quantities of financial input are being diverted for research in this area. As a consequence of this huge financial support for diabetic research, the literature is flooded with various
reports on the different aspects of the course, pathophysiology and treatment of diabetes mellitus. It is neither possible nor necessary to cite the entire literature available on diabetes mellitus in this review. Hence the present review will concentrate only on the alterations of brain catecholamines in diabetic state both in experimental animals and in human post-mortem studies.

Though the literature on diabetes in general is extremely vast, the studies on brain biogenic amines in diabetic state is relatively sparse and recent. The probable cause for this anomaly is the fact that earlier works were mainly concentrating on alleviating the dreadful consequences of diabetes mellitus and hence the subtle changes in the neural functions were ignored.

Insulin dependent diabetic patients have been reported to experience various affective disorders (Burch, 1949 and Sterns, 1953). Eventhough their diabetic state is well controlled by insulin administration (Murawski et al., 1970; Dupuis, 1980; and Rodin, 1983) a common phenomena observed in these patients is that of mood changes in which the individual experiences alternating periods of depression and normal affect or even elation. Based on this clinical clue, the initial investigators examined the neurochemical changes that occur during experimental diabetes mellitus in animals (Mc Kenzie and Trulson, 1978a). These workers have shown decrease in brain tryptophan concentration with unaltered 5-hydroxytryptamine (5-HT) metabolism in all groups of diabetic animals maintained on different feeding schedules to control for the effects of hyperphagia. This deficit in brain tryptophan was reversed within 2 hours after insulin administration. Their results were taken
to indicate that brain tryptophan and 5-HT metabolism following insulin injections is not a response to the stress of decreased cerebral glucose utilization or hypoglycemia and their experiments have conclusively proved that one requirement for normal brain tryptophan concentrations is a normal level of circulating insulin. The decreased brain tryptophan concentration is probably due to the altered ratio of tryptophan / neutral amino acids in plasma (Try / ΣNAA ratio). In a subsequent work the same authors have shown that this increased uptake of tryptophan in the brain in insulin treated diabetic animals is not due to a direct action of insulin in the brain tissue (McKenzie and Trulson, 1978a, 1978b). The probable impetus for McKenzie and Trulson work is from the previous work of Fernstrom and Wurtman (1971) who have shown that in the rat, the injection of insulin or consumption of carbohydrate causes sequential increase in the concentration of tryptophan in the plasma and the brain, and of serotonin in the brain. Serotonin containing neurons may thus participate in systems whereby the rat brain integrates information about the metabolic state in its relation to control of homeostasis and behavior.

Crandall and Fernstrom (1980) investigated the acute changes in brain tryptophan and serotonin after carbohydrate or protein ingestion by diabetic rats and showed that in normal fasting rats intubating with glucose did not alter serum tryptophan, but it did reduce serum concentrations of large neutral amino acids - tryptophan competitors for brain uptake. The serum ratio of tryptophan to some of these competitors, which predicts brain tryptophan uptake was thus increased. Brain serotonin and its precursor tryptophan and its metabolite 5-HIAA levels were also increased. Since
serotonin is a neurotransmitter such increases are potentially important and may be involved in modulating the brain functions. In contrast, glucose intubation of fasting STZ diabetic rats, elicited only a small increase in the serum tryptophan ratio. Brain tryptophan increase slightly; no changes occurred in brain serotonin or in 5-hydroxy indole acetic acid (5-HIAA). Similar effects were noted when fasting diabetic rats consumed a single carbohydrate meal. However, brain indoles did increase after carbohydrate ingestion in diabetic rats that received an insulin injection at the time food was presented. These authors have also studied effects of ingesting a protein containing meal. In normal rats consumption of this meal increased the serum tryptophan ratio slightly without changes in brain tryptophan and serotonin levels. In diabetic rats ingestion of protein containing meal often lowered the serum tryptophan ratio accompanied by a fall in brain tryptophan. However, brain hydroxy-indoles did not show any change in these animals. Based on these observations these authors concluded that the absence of carbohydrate induced increment in brain indole levels follows indirectly from the absence of insulin induced raise in the serum tryptophan ratio. The diabetic rats inability to experience normal carbohydrate induced increment in brain serotonin, probably suggest that brain functions normally dependent on such neurochemical signals, may be abnormal.

Crandall et al. (1981) measured the rate of serotonin synthesis in the brains of normal and STZ-diabetic animals using both the rate of 5-HIAA after pargyline treatment. In this study they have shown the serotonin synthesis was significantly reduced in diabetic rats and the reduction of synthesis may be a direct result of lowered brain tryptophan levels in diabetic
rats. Based on these observation they have suggested that the reduction in serotonin synthesis in the diabetic rat brain is perhaps associated with reduced transmitter release.

Despite these animal findings, post-mortem evidence indicates increased 5-HT synthesis in human diabetic coma. Jellinger and Riederer (1978) reported raised 5-HT and 5-HIAA concentrations in the post-mortem brains of patients with diabetic coma. To elucidate the cause for this contradiction Curzon et al. (1982) determined free fatty acids and free and total tryptophan in plasma of (A) ketoacidotic diabetics (B) well controlled diabetics and (C) non diabetics. Cerebrospinal fluid (CSF) tryptophan and 5-HIAA were measured in groups (A) and (C) as respective indices of the availability of tryptophan to the CNS and of 5-HT synthesis therein. Determination were also made in plasma and CSF of the dopamine precursor-tyrosine and in the CSF of dopamine metabolite homovanillic acid (HVA). This study has shown that patients during the recovery from an episode of ketoacidotic coma has raised blood glucose, plasma free fatty acids and plasma free tryptophan concentrations. Plasma total tryptophan was decreased. Well controlled diabetics showed normal values. The ketoacidotic patients had increased lumbar CSF tryptophan and 5-HIAA concentrations. Plasma tyrosine, CSF tyrosine and HVA concentrations were normal in both diabetic groups. These findings according to these authors were somewhat similar to that seen in uremic and hepatic encephalopathy and also to changes seen in rats with STZ-diabetes. Based on these findings Curzon et al. (1982) suggested that these biochemical changes could be involved in the sensorial clouding, progressing to coma which occurs in these disorders.
However altered indole metabolism is only part of the widespread metabolic disturbances they cause. It may well play a role in the altered behavior but is hardly likely to be solely responsible for it as large increase of tryptophan intake in normal subjects only moderately impair consciousness.

Since genetically diabetic rats resemble more closely human diabetic condition than experimentally induced diabetic animals, Kwok et al. (1985) studied the concentration of 5-HT and 5-HIAA in the brain of spontaneously diabetic male wistar rats. These rats showed a marked increase in blood and urine glucose, polydipsia, polyuria and weight loss that had an onset of diabetes 11 - 23 days earlier. Controls were littermates with no hyperglycemia, glycosuria or weight reduction. Spontaneously diabetic rats showed a significant reduction of 5-HIAA in the olfactory tubercle. No change was found in the concentration of 5-HT, indicating marked reduction in mesolimbic 5-HT metabolism. Based on these observation they have suggested that this reduction could be consequence of reduction in 5-HT synthesis. These authors have also estimated DA, DOPAC and HVA, the results of which will be cited later.

Trulson et al. (1986) studied the rate of brain serotonin synthesis and turnover in STZ-diabetic rats using three separate methods: The rate of 5-hydroxytryptophan accumulation following decarboxylase inhibition, 5-HIAA levels following monoamine oxidase inhibition and the rate of 5-HIAA accumulation following blockade of acid transport. Each of the three methods revealed that 5-HT synthesis and turnover is decreased by 44-71% in diabetic rats with plasma glucose levels ranging between 500-600 mg%.
addition, the levels of free and bound plasma tryptophan and free aminoacids were found to be the same in the control and diabetic rats. Since diabetic rats exhibited a 40% decrease in brain tryptophan, the free tryptophan levels in diabetic rats. These authors suggested the possibility of altered 5-HT levels in the brain of human diabetic patients could be responsible for various behavioral and psychological changes that occur under these circumstances.

From the foregoing review it becomes clear that most of the previous work were using STZ-induced diabetic animal model. It is also clear that the mechanism of action and the metabolic consequences of alloxan and STZ are strikingly different. Considering these striking contrast between metabolic patterns of STZ and alloxan induced diabetes including levels of plasma nonesterified fatty acids (NEFA), blood ketones, heart glycogen and hepatic enzymes, Mello et al. (1988) examined these two models of diabetics on brain levels of indoleamines in addition to plasma glucose and NEFA. This study has demonstrated that fasted STZ-induced diabetic animals also have increased NEFA levels. Alloxan and fasted, streptozotocin-induced diabetic rats showed significant increase in brain indoleamine concentrations, whereas fed STZ-induced diabetic rats had unchanged levels of the same compound. Levels of brain indoleamines exhibited a strong positive correlation with Wet-Dog Shakes (an index of 5-HT activity). The increased content of brain indoleamines in alloxan and fasted STZ - induced diabetic rats may be related to the increased NEFA plasma levels seen in the same animals. The positive correlation demonstrated between NEFA and 5-HT levels in this study support the above concept. These authors are of the opinion that alloxan
induced-diabetes may represent a useful model for studying the various behavioral changes known to occur in diabetes.

Broderick and Jacoby (1988) using in-vivo voltametry to measure synoptic release of striatal DA and serotonin after the administration of aminoacid L-tryptophan to STZ-induced diabetic rats, reported that rat striatal serotonin release predictably increased after L-tryptophan injection in non-diabetic rats. A further increased striatal serotonin release was seen in acutely diabetic rats. However, chronically diabetic rats responded to L-tryptophan with a dramatic and significant decrease in striatal serotonin release (the results of DA release will be cited later). Based on these results the authors concluded that the progression of diabetics is associated with an impaired ability to release primary neurotransmitter in the rat brain.

An analysis of the past literature has shown that majority of the previous work is directed towards understanding 5-HT alterations in the brain of diabetic animals. The work on other brain biogenic amines in experimental diabetic animals is relatively sparse and will be reviewed presently.

Since dopamine is also implicated in the etiology of behavioral and mood disorders as well as in emotional disturbances sometimes associated with diabetes, Lozovsky et al. (1981) studied the dopamine receptor binding of $^3$H spiperone - a dopamine receptor ligand in alloxan and STZ - diabetic rats. In this study they have shown the binding of $^3$H spiperone to striatal membranes was increased 30-35% in rats made diabetic with alloxan or STZ. Binding of this ligand was normal in rats made diabetic with alloxan but
treated with insulin. Based on these results they have concluded that the number of dopamine receptors and central dopaminergic transmission may be altered in diabetes.

Monoamine oxidase (MAO) is a mitochondrial enzyme responsible for oxidative deamination of a variety of biogenic amines. Any change in this enzyme activity alters the neurotransmitter function and hence MAO has been implicated in disorders such as affective disorders, aggressive behavior etc. Based on this available evidences Mayanil et al. (1982) studied changes in monoamine oxidase activity in rat brain at various time intervals after the onset of diabetes. It was observed that MAO activity was decreased at early time intervals after diabetes followed by a recovery in all 3 regions of the brain. A reversal of the effect was observed with insulin administration to the diabetic rats. These authors attributed the early decrease in MAO activity to decreased synthesis of catecholamines during the early stages of diabetes.

Based on the multiple effects of glucose on dopamine system Trulson and Himmel (1983) investigated the dopamine synthesis in both the nigro-striatal and mesolimbic system in diabetic rats with blood glucose levels 5-6 times higher than those in normal rats. They have shown the rate of accumulation of 3, 4-dihydroxyphenylalanine following decarboxylase inhibition and of HVA following probenicide treatment were significantly decreased in STZ-diabetic rats. These changes were observed in both striatum and limbic forebrain. The $B_{\text{max}}$ for $H^3$ spiroperidol receptor binding was significantly increased in both brain regions. All these neurochemical changes were reversed by insulin replacement therapy. These authors are of the
opinion that it is uncertain whether the neurochemical changes are really attributable to chronic hyperglycemia or some other aspect of diabetic state which could play a role in the manifestations of these neurochemical changes.

Trulson and Himmel (1985) in a subsequent work investigated the status of nor-adrenergic system in STZ-diabetic rats in order to elucidate the role of nor-adrenergic system in mood disorders of diabetic individuals. In this work, they have shown that administration of insulin produced a significant decrease in forebrain norepinephrine (NE) and a significant increase in the major metabolite of NE, 3- methoxy-4-hydroxyphenyl glycol sulfate (MOPEG-SO₄) in rats. STZ-induced diabetes produce the opposite effect resulting in an increase in forebrain NE and a decrease in MOPEG-SO₄. In addition, insulin increased and diabetes decreased the turnover rate of NE as measured by the rate of decrease of NE following inhibition of tyrosine hydroxylase (TH) by alpha-methyl-p-tyrosine. All these effects in diabetic rats were reversed by insulin replacement therapy. These authors are of the opinion that these findings may have the implications for the clinical observations in type I diabetic patients who show characteristic fluctuations in mood.

In a study which was designed to delineate the relationship between neurotransmitter, behavioral and hormonal abnormalities in an animal model of diabetes mellitus. Bitar et al. (1986) reported changes in monoamine metabolism in the CNS of adult male and female diabetic rats. In this study, Bitar et al. (1986) measured the activities of tyrosine hydroxylase and of cholin-acetyl-transferase in various brain regions of control and
STZ-treated Sprague-Dawley rats. It was noted during the course of diabetes, progressive decrease in the activity of tyrosine hydroxylase and marked increase in the concentration of NE in several brain regions including thalamus, hypothalamus, medulla and midbrain. The concentration of DA and 5-HT in various brain regions of the 10-30 days diabetic rats were generally not significantly different from the controls. Concentrations of the acidic metabolites of these neurotransmitters, dihydroxyphenylacetic acid and 5-HIAA were however greatly reduced. The activity of cholin-acetyl-transferase, a marker of pre-synaptic cholinergic neuron activity remained unaltered during the course of diabetes. Based on these data the authors concluded that uncontrolled diabetes is associated with significant disturbance of brain monoamine metabolism.

While studying genetically diabetic rats, Kwok et al. (1985) reported a significant reduction of DOPAC in the striatum, and DOPAC and HVA in the olfactory tubercles, no change was found in the concentration of DA. Thus the marked reduction in striatal and mesolimbic dopamine metabolism in spontaneously diabetic rats could be the consequence of a reduction in the formation of DA.

Chu et al. (1986) hypothesized that alterations in physiological functions of diabetic animals could be due to changes in brain monoamine metabolism seen in this state. To test this hypothesis these authors have studied several physiological functions (including thermoregulation, motoractivity and antinociception) and the monoamine content of different brain regions in untreated STZ-diabetic, insulin treated STZ-diabetic and
healthy control rats. These diabetic animals while showing a number of physiological deficits in the parameter studied also had a lower catecholamine level in the hypothalamus and a higher level in corpus striatum. The alterations in brain monoamine content and the physiological deficits observed were reversed after insulin replacement therapy. The data obtained by them suggests that alterations in various autonomic somatosensory and motor neural functions of untreated STZ-diabetic rats correlated with a reproducible pattern of monoamine content in various brain regions (a pattern that differed from that observed in healthy control rats), and that both the altered neural function and the altered brain monoamine pattern were reversed after insulin therapy. However, a cause-and-effect relationship has not been established in this study. It is not known whether the changes in brain monoamines or in the studied physiological parameters were directly related to changes in insulin levels, changes in blood glucose, or to a changes in a metabolic parameter not studied (such as lactate, pyruvate, sodium, potassium etc.) which in turn is influenced by glycemic control or by circulating insulin levels.

Most of the experimental studies on central neurotransmitter concentrations in diabetic animals have been measured no sooner than one month after the onset of diabetes and very little information is available about the effect of diabetes on central neurotransmitter levels at the beginning of the disease. Since clinically it is important to determine whether alterations of the central neurotransmitter concentrations occur only after long periods of uncontrolled diabetes or whether even a short period of uncontrolled diabetes can cause specific neurochemical disturbances in the brain,
Wesselmann *et al.* (1988) determined the catecholamine concentrations in spinal cord, cerebellum, pons medulla and the remaining brain 6 and 52 days after the onset of diabetes. These authors have reported that 6 days after the induction of diabetes, norepinephrine levels were significantly increased only in cerebellum, which was further increased on the 52nd day. These effects were not seen when the diabetic animals received insulin replacement therapy showing thereby even a short period of uncontrolled diabetes can result in significant alterations in central NE levels. These alterations are progressive.

Much earlier alterations in dopamine and serotonin release from corpus striatum of diabetic rats was reported by Broderick and Jacoby (1988) who have studied dopamine and serotonin release from rat striatum at a short-term or acute (3 days) interval and a long term or chronic (3-7 weeks) interval after the induction of diabetes. This study, which was done in age, sex and food matched controls showed that L-tryptophan decreased dopamine release from rat striatum in non-diabetic rats. The decreased striatal dopamine release, after L-tryptophan administration exacerbated in acutely diabetic rats and further exacerbated in chronically diabetic rats. Results of this study has also shown that in acutely diabetic and normal rats L-tryptophan administration reduced striatal DA and increased striatal serotonin release, whereas in chronically diabetic rats the release of both biogenic amines were decreased.

Chen and Yang (1991) investigated the effects of short and long-lasting diabetes mellitus on brain monoamines in various brain regions of 3, 50 and 100 days diabetic mice. This study has shown an increase in the
content of NE in pons-medulla and striatum in short-term (3 days) diabetic mice, which persisted till 100 days. In the hypothalamus and cortex the increase of NE was observed in both 50 and 100 days diabetic mice, whereas in cerebellum increase in NE was seen only in 100 days diabetic mice. The concentration of dopamine was increased in the striatum both in short-term and long-term (50 and 100 days) diabetic mice, that of pons-medulla and cortex was increased only in the long-term diabetic mice. Concentrations of the acidic metabolites of DA, dihydroxyphenyl acetic acid and HVA were decreased in the hypothalamus, hippocampus and striatum, while increased in pons-medulla and cortex. 5-HT concentration was increased in hypothalamus, hippocampus, pons-medulla and cortex progressively from short-term to long-term diabetic mice. However, the concentration of its acidic metabolites 5-HIAA, was decreased in hypothalamus, hippocampus, striatum, pons-medulla and cortex. These data suggests that the biogenic amine disturbance in diabetes mellitus was not generalized but related to some specific areas of the brain and some of these alterations were progressive from short-term to long-term diabetes.

Dash et al. (1991) investigated the effect of hyperglycemia due to experimental diabetes on acetyl cholinesterase and catecholamine levels in the rat brain and heart. Experimental diabetes causes a decrease in the activity of acetyl cholinesterase in the brain regions and heart; changes in the heart being more significant than the brain. Significant increase in the levels of catecholamines were also found in the brain regions in diabetes. Insulin administration reversed all these effects. Based on these results, these authors have suggested that impaired glucose oxidation and glucose transport might
cause specific alterations in neurotransmitter level thereby affecting blood brain barrier transport, thus causing brain dysfunction in diabetes mellitus.

Bellush et al. (1991) investigated the functional significance of biogenic amine alterations in STZ-induced diabetic rats. These experiments examined the effects of restraint stress on DA, 5-HT and their principle metabolites DOPAC and 5-HIAA respectively in four brain regions as well as on plasma corticosterone concentration and behavior in STZ-diabetic rats and non-diabetic controls. Diabetic rats and widespread reductions in DA and 5-HT turnover (DOPAC/DA and 5-HIAA/5-HT ratio's). Restraint led to equivalent increases in DA turnover in diabetics and non-diabetics and attenuated increases in 5-HT turnover in diabetic rats. Corticosterone levels of diabetics and non-diabetics measured under resting conditions did not differ. Relative to these measures only diabetics had elevated corticosterone when either restraint or kept in the same room with restrained rats with food and water removed. Open field exploration was suppressed by restraint in diabetics only. All diabetic rats showed decreased locomotion in a novel environment which was normalized during a second exposure to the apparatus. Together, these results suggest that diabetes induced disruptions in open field activity are related to anxiety rather than to motor or energy deficits and may be related to impaired 5-HT and corticosterone systems.

Gupta et al. (1992) studied the levels of epinephrine, norepinephrine and dopamine and the activities of tyrosine hydroxylase and monoamine oxidase in four regions of rat brain during alloxan-induced hyperglycemia and insulin-induced hypoglycemia. The results of this study demonstrated
significant increase in the activities of the metabolizing enzymes and levels of catecholamines during experimental conditions. The levels of catecholamines were highest in the cerebral hemisphere, the region associated with high activities of the metabolizing enzymes. Insulin-induced hypoglycemia caused a decrease in the activities of the metabolizing enzymes followed by the recovery within 2 hours.

Salkovic and Lackovic (1992) after an in-depth study of brain D₁-dopamine receptors in alloxan-diabetic rats reported decreased D₁ receptor density in the striatum of the diabetic animals. No change in the receptor density was observed in the olfactory tubercle. This study showed a region specific changes in brain dopamine D₁ receptors in alloxan-diabetes.

Tasaka et al. (1992) measured brain catecholamine concentration in experimentally made hyperosmola diabetic, diabetic and normal control rats, in order to clarify the metabolic changes of the brain in these states. Diabetes was induced by STZ, hyperosmolarity was achieved through deprivation of water for 50 hours prior to experimentation. DA, NE and E concentrations were measured in the left cerebral cortex, hypothalamic thalamic area, cerebellum and medulla oblongata. DA and NE concentrations were significantly elevated in cerebral cortex, hypothalamic thalamic area and cerebellum of the dehydrated hyperosmolar diabetic rats. In diabetic rats with high blood sugar level the NE concentration was significantly elevated in the cerebral cortex, cerebellum and medulla and these changes generally paralleled the increase in fasting blood glucose. It was concluded that hyperosmolarity due to dehydration contributed to these changes and the
changes in brain catecholamines may be involved in the nervous system disturbances that occur in the dehydrated hyperosmolar diabetes and severe diabetes.

It is generally believed that the alterations in the brain biogenic amines in experimental diabetes are due to the diabetic state. However, it must also be remembered that no experimental animal model of diabetes mellitus is equivalent of the human diabetic condition. In this connection, it is pertinent to review the work of Lackovic and Salkovic (1990). These authors have demonstrated that one week after an intracerebroventricular administration of non-diabetogenic dose of STZ (5-20 mg/kg) or alloxan (20 mg/kg) changes in brain monoamines were similar to those observed in diabetic animals. This observation apparently suggest that the CNS effect of STZ or alloxan is not necessarily related to a diabetogenic β-cytotoxic action of these substances.