PLASMA LEVEL OF BETA-ENDORPHIN IN CONTROLLED AND UNCONTROLLED DIABETICS

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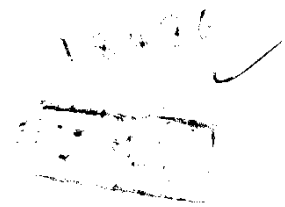

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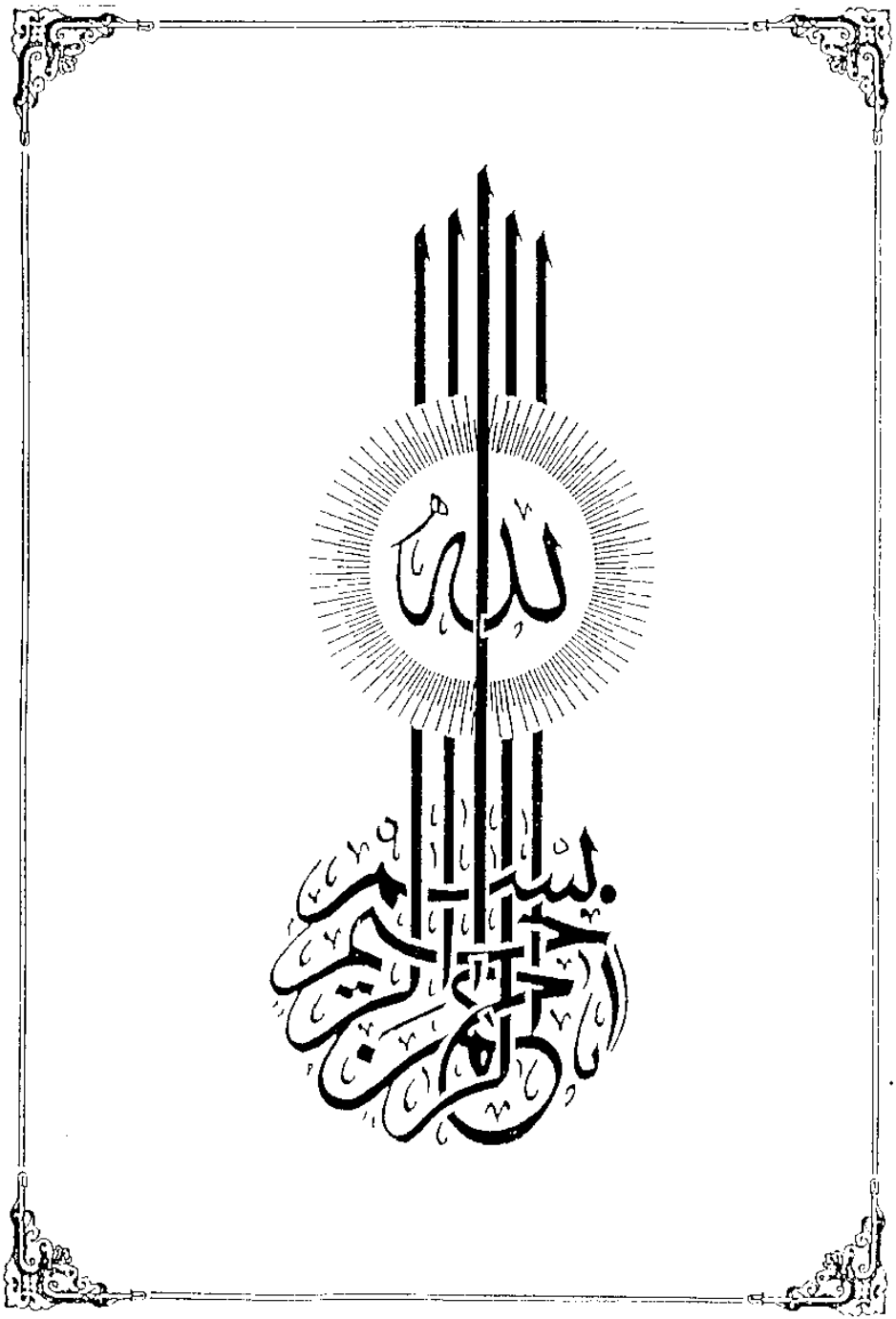

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The demonstration, several years ago, of the existence of opiate receptors in the central nervous system and the subsequent demonstrations of endogenous opiate peptides, had generated considerable interest.

Among the isolated peptides, B-endorphin was found to be the most potent in analgesic activity (Loh et al., 1976 and Bunney et al., 1979), opiate receptor binding (Lazarus et al., 1976) and behavioral effect (Meglio et al., 1977; Miller and Pickel, 1980).

The importance of endorphins in neuroendocrine regulation appeared well established. They stimulated the release of growth hormone and prolactin (Rivier et al., 1977; Chihara et al., 1978; Kato et al., 1978 and Martin et al., 1978) as well as adrenocorticotropin (Guillemin et al., 1977 and Morley, 1981). In contrast, they inhibited the release of luteinizing hormone, follicle stimulating hormone (Cicero et al., 1976; Bruni et al., 1977) and thyrotropin (Krulich et al., 1977; Schachter, 1981). Significant amounts of B-endorphin were found in patients with Nelson's syndrome, Cushing's disease and addison's disease (Suda et al., 1978; Krieger et al., 1981).

Accordingly, it was obviously of interest to estimate the level of B-endorphin in a major endocrine disorder as Diabetes Mellitus.

The well established relation of endorphins to carbohydrate metabolism (Borison et al., 1962; Leslie et al., 1979; Reid and Yen, 1980 and Van loon and Appel, 1981) and the relation of both diabetes mellitus and B-endorphin to stress (Rossier et al., 1977; and Bloom et al., 1980) had tempted us to study the B-endorphin level in plasma of diabetics.

So, the aim of this work is to try to correlate diabetes mellitus and carbohydrate homeostasis to plasma B-endorphin level.

REVIEW OF THE LITERATURE

ETIOLOGY AND PATHOGENESIS OF DIABETES MELLITUS

I. ETIOLOGY

Minkowski and Von Mering in 1886 by producing diabetes mellitus in dogs by total pancreatectomy, suggested to early workers that diabetes mellitus was the result of a degenerative process involving the pancreatic B-cells. Recent studies had directed attention to many pathologic processes including infectious etiologies (Notkins,1977), autoimmune phenomena (Nerup et al., 1976, Maclaren et al., 1977) and target tissue defects (Flier et al., 1979). At the present time, it appeared likely that the condition known as diabetes mellitus could be produced by nearly all of the commonly recognized pathologic processes: infections, toxins, immune reactions, inflammatory necrosis of the pancreas, genetic defects of the "one gene one protein" type and rarely neoplastic phemomena e.g. glucagonoma.

Felig and Baxter (1981) reported that diabetes had long been classified on the basis of specific clinical features into two major types:- juvenile-onset and maturity-onset. The large overlap of age of onset among the two types indicated that those terms were often inaccurate. Accordingly, a new classification was recommended by the National Institutes of Health in July 1979 and by the WHO

Expert Committee in 1980. (TABLE I presented the recent classification of diabetes mellitus).

Spontaneous Diabetes

In over 90% of cases, diabetes was a spontaneous disorder which could not be ascribed to some other more primary disease process (Felig and Baxter, 1981). Two major types of spontaneous diabetes were recognized:- Type I or insulin-dependent diabetes (formerly called juvenile-onset diabetes) and type II or insulin-independent or non-insulin-dependent diabetes (formerly called maturity-onset diabetes). The contrasting clinical, genetic, immunologic characteristics were summarized in TABLE II. Maturity-onset diabetes of young people was designated as MODY and in that case, there was neither ketosis nor insulin dependence but asymptomatic hyperglycemia observed in young subjects and associated with autosomal dominant transmission.

The major factors which had been identified to produce spontaneous diabetes were inheritance, viral infections, autoimmunity and nutrition.

TABLE I- Classification of Diabetes Mellitus

1- Spontaneous diabetes mellitus

   a- Type I or insulin-dependent diabetes (formerly called juvenile-onset diabetes).

   b- Type II or insulin-independent diabetes (formerly called maturity-onset diabetes).

2- Secondary diabetes

   a- Pancreatic disease (pancreoprivic diabetes, e.g., pancreatectomy, pancreatic insufficiency, hemochromatosis).

   b- Hormonal: excess secretion of contrainsulin hormones (e.g., acromegaly, cushing's syndrome, pheochromocytoma).

   c- Drug induced (e.g., potassium-losing diuretics, contrainsulin hormones, psychoactive agents, diphenyl-hydantoin).

   d- Associated with complex genetic syndromes (e.g., ataxia telangiectasia, Laurence-Moon-Biedl syndrome, myotonic dystrophy, Friedrich's ataxia).

3- Impaired glucose tolerance (formerly called chemical diabetes, asymptomatic diabetes, latent diabetes and subclinical diabetes): normal fasting plasma glucose and 2-h value on glucose tolerance test $>$ 140 mg/dl but $<$ 200 mg/dl.

4- Gestational diabetes: glucose intolerance which has its onset in pregnancy.

Source: National Diabetes Data group: Diabetes 28: 1039, 1979.

ABLE II. Clinical, genetic and immunologic characteristics of Insulin-Dependent (Type I) and Insulin-Independent (Type II) Diabetes.

	Insulin-dependent diabetes	Insulin-Independent diabetes
Synonyms	Type I, juvenile-onset diabetes	Type II, maturity-onset diabetes
Age of onset	Usually 30	Usually 40
Ketosis	Common	Rare
Body weight	Non obese	Obese (80%)
Prevalence	0.5%	2-4%
Genetics	HLA-associated, 40-50% concordance rate in twins	Non-HLA-associated, 95-100% concordance rate in twins
Heredofamilial tendency	Negative family history	Positive family history in a large percentage of cases
Circulating islet cell antibodies	50-85%	10%
Treatment with insulin	Necessary	Usually not required
Complications	Frequent	Frequent

1- Genetic factor:

A familial clustering of diabetes had long been recognized. In large population surveys, the prevalence of the disease among relatives of diabetic patients had been reported as four to ten-fold greater than in control subjects. In addition, diabetes might occur with unusual high frequency in Pima Indians and Japanese (Sasaki et al., 1982). More compelling evidence for genetic transmission was provided by twin studies (Tattersall and Pyke, 1972). Among monozygotic twins, the concordance rate for diabetes varied from 45 to 96%.

The advent of HLA (Human Leucocyte Antigen) data provided a completely new insight into the likely genetic basis to type I diabetes and also the distinction from type II diabetes became clear as there was no HLA association with that disease (Nerup et al., 1974). The HLA complex in humans consisted of a cluster of four gene loci (designated A, B, C, D and DR) on the sixth chromosome which determined the major histocompatibility antigens. Among type I (insulin-dependent) diabetics, a significantly increased frequency of HLA antigens B_8, BW_{15}, DW_3 and DW_4 had been observed (Ganda and Soeldner, 1977; Rotter and Rimoin, 1978).

The presence of one of those haplotypes increased the relative risk for juvenile-onset diabetes by two to six-fold. In marked contrast, no association between specific HLA types and type II diabetics had been observed.

The various HLA alleles might not themselves be responsible for the predisposition to diabetes, but might exist in linkage disequilibrium with other genes more directly related to diabetes susceptibility.

Recently, it had been shown that an unusual genetic type BfF1 of properdin factor B was present in 22.6% of patients with insulin-dependent diabetes compared to 1.9% of the general population (Raum et al., 1979).

The linkage of the HLA system to the specific immune response genes had raised the possibility that the diabetic genotype operated by permitting the interaction of a virus with specific antigens on the beta cell membrane (Craighead, 1978).

Studies comparing the inheritance pattern of MODY (a subdivision of type II diabetes) and type I diabetes provided additional evidence of genetic heterogeneity

(Fajans et al., 1978). In the families of MODY diabetics, several features pointed to autosomal dominant inheritance:

(i) There was vertical transmission of diabetes through three generations in almost half the families,

(ii) 85% of affected patients had an affected parent and,

(iii) One-half of the siblings were diabetic.

2- Viral infections and other environmental factors

The evidence for a viral etiology of diabetes derived from histologic, epidemiologic and more recently direct studies of transmission of diabetes from a human patient to an experimental animal (Yoon et al., 1979).

The histologic appearance of the islets in patients dying with type I diabetes was characterized by infiltration with mononuclear cells particularly lymphocytes and degeneration of islet cells. The presence of that inflammatory response termed "insulitis" was compatible with a viral, and/or autoimmune process. Further circumstantial evidence for a viral etiology was provided by the seasonal variation in the onset of type I diabetes, the peak incidence occuring in late summer or winter with a paucity of cases appearing in spring or early summer.