Plasma Levels of β-Endorphin and Adrenocorticotropic Hormone in IDDM and NIDDM

MARK N. FEINGLOS, MD
RICHARD S. SURWIT, PHD
CYNTHIA C. MCCASKILL, RN
SUZANNE L. ROSS, PHD

There has been considerable discussion regarding the role of CNS in the etiology and control of non-insulin-dependent diabetes mellitus (NIDDM; 1,2). One particular area of study has been the possible contribution of endogenous opiates to disordered carbohydrate metabolism (3–5). Vermes et al. (6) found that patients with NIDDM had significantly higher levels of peripherally circulating immunoreactive β-endorphin and adrenocorticotropic hormone (ACTH) than patients with insulin-dependent diabetes mellitus (IDDM) and control subjects. As part of our investigation of the role of CNS in carbohydrate metabolism, we repeated these measurements on a group of our own patients, with different results.

Diabetic patients visiting the Duke University diabetes clinic for routine appointments gave informed consent, and a single venipuncture was performed between 900 and 1130. Subjects consisted of four men and eight women with IDDM (mean ± SD age 36.5 ± 7.3 yr, duration of diabetes 17.4 ± 11.8 yr, % ideal body wt 105.5 ± 9.8%) and seven men and five women with NIDDM (age 50.6 ± 9.7 yr, duration of diabetes 4.6 ± 4.1 yr, % ideal body wt 138.0 ± 23.3%). Patients were excluded if they used an adrenergic agonist or antagonist, corticosteroid, or centrally acting drug, or had a history of mental retardation or psychiatric illness. In the NIDDM group, two patients were diet controlled, four patients used oral hypoglycemic agents only, and six patients used insulin (with or without oral agents). Samples were assayed for plasma glucose (measured by autoanalyzer, Beckman, Brea, CA), insulin (radioimmunoassay [RIA] kit, Cambridge Medical, Cambridge, MA), β-endorphin (RIA kit, Nichols, San Juan Capistrano, CA), ACTH (high-sensitivity ACTH IRMA, Nichols), and plasma cortisol (specific RIA with high-performance liquid chromatography–purified tritiated ligands, antiserum, and standards were purchased from Radioassay System, Carson City, CA).

There were no significant differences in plasma glucose, β-endorphin, or ACTH between the two groups (Table 1). For unknown reasons, plasma cortisol was significantly higher in patients with IDDM. The IDDM group, as is typical of our population, was also significantly younger ($P = 0.0006$), weighed less (by % ideal body wt, $P = 0.0004$), and had a longer duration of disease ($P = 0.003$).

With use of the effect size and variance reported by Vermes et al. (6), 12 patients/group provided a statistical power of 0.80 for $P < 0.05$ (2 tailed). Thus, although we had sufficient statistical power to detect an existing difference, we found no variability in β-endorphin or ACTH in our patient sample. It is possible that our population is different from the one previously reported. Recent evidence, looking at other parameters, suggests that the NIDDM population is heterogeneous (7,8). Further study is needed to determine whether this is indeed true in regard to endogenous opiate levels.

Table 1—*Plasma levels of glucose, β-endorphin, ACTH, and cortisol in patients with IDDM and NIDDM*

	IDDM	NIDDM
GLUCOSE (MM)	12.5 ± 1.73	9.9 ± 0.92
B-ENDORPHIN (PM)*	10.04 ± 2.4	9.93 ± 2.0
ADRENOCORTICOTROPIC HORMONE (FM)†	6.3 ± 0.85	6.7 ± 0.85
CORTISOL (NM)	51.7 ± 6.60‡	27.8 ± 3.04‡

Results are means ± SE for $n = 12$ patients/group. IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.
*8.4 ± 1.4 pM for nondiabetic patients.
†1.98–11.45 fM for nondiabetic patients.
‡$P < 0.01$, IDDM vs. NIDDM by Wilcoxon's rank-sum test.

FROM THE DEPARTMENT OF MEDICINE, DIVISION OF METABOLISM, ENDOCRINOLOGY AND GENETICS, AND THE DEPARTMENT OF PSYCHIATRY, DIVISION OF MEDICAL PSYCHOLOGY, DUKE UNIVERSITY MEDICAL CENTER, DURHAM, NORTH CAROLINA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO MARK N. FEINGLOS, MD, ASSOCIATE PROFESSOR OF MEDICINE, DIVISION OF METABOLISM, ENDOCRINOLOGY AND GENETICS, BOX 3921, DUKE UNIVERSITY MEDICAL CENTER, DURHAM, NC 27710.

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Mutations in Insulin-Receptor Gene

Val^{996} Allele in White NIDDM Patients

ANTONIO PORCELLINI, MD
SERGIO COCOZZA, MD
ANTONELLA MONTICELLI, MD
LUIGI PIANESE, BS
GABRIELE RICCARDI, MD
ASSIAMIRA FERRARA, MD
STELIO VARRONE, MD

The insulin-receptor (IR) gene plays a critical role in allowing cells to respond to insulin (1), and insulin resistance is a prominent feature of non-insulin-dependent diabetes mellitus (NIDDM; 2). The involvement of the IR defects in the etiology of diabetes mellitus has been suggested by the findings of mutations in the IR gene in rare patients with genetic syndromes of severe insulin resistance (3–12). Odawara et al. (7) have described a case of young Japanese male with insulin resistance and acanthosis nigricans in which valine is substituted for glycine at position 996 (GTC instead of GGC) in the tyrosine kinase domain of the IR gene. Whether this mutation also contributes to the etiology of the common forms of NIDDM is unknown. Therefore, we determined the prevalence of the Val^{996} allele of the IR gene in a population of white NIDDM patients.

We studied a population of 103 NIDDM patients referred to the Diabetic Clinic of our Medical School. Diagnosis of NIDDM was made according to National Diabetes Data Group criteria. All subjects gave their informed consent to participate in the study. Subjects had a mean ± SE age of 56.9 ± 1.06 yr and a body mass index of 28.12 ± 0.45 kg/m^2. Their diabetes duration was 12.97 ± 0.85 yr. Forty-three were men and 60 were women. We used a modification of the polymerase chain reaction (PCR) procedure that permits the rapid identi-

FROM THE DEPARTMENT OF CELLULAR AND MOLECULAR BIOLOGY AND PATHOLOGY "L. CALIFANO" AND CENTRO DI ENDOCRINOLOGIA ED ONCOLOGIA SPERIMENTALE, NATIONAL RESEARCH COUNCIL, NAPLES; AND THE INSTITUTE OF INTERNAL MEDICINE AND METABOLIC DISEASE, 2ND MEDICAL SCHOOL, UNIVERSITY OF NAPLES, ITALY.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO SERGIO COCOZZA, MD, DIPARTIMENTO DI BIOLOGIA E PATOLOGIA, CELLULARE E MOLECOLARE "L. CALIFANO," VIA S. PANSINI 5, 80131 NAPLES, ITALY.