Chem 32:421–28, 1989
2. Fujiwara T, Yoshioka S, Yoshioka T, Ushiyama I, Horikoshi H: Characterization of new oral antidiabetic agent CS-045: studies in *KK* and *ob/ob* mice and Zucker fatty rats. *Diabetes* 37:1549–58, 1988
3. Reaven GM: Insulin secretion and insulin action in non-insulin-dependent diabetes mellitus: which defect is primary? *Diabetes Care* 7 (Suppl. 1):17–24, 1984
4. Olefsky JM: Pathogenesis of insulin resistance and hyperglycemia in non-insulin-dependent diabetes mellitus. *Am J Med* 79 (Suppl. 3B):1–7, 1985
5. Gerich JE: Oral hypoglycemic agents. *N Engl J Med* 321:1231–45, 1989
6. Fujita T, Sugiyama Y, Taketomi S, Shoda T, Kawamatu Y, Iwatsuki H, Suzuoki Z: Reduction of insulin resistance in obese and/or diabetic animals by 5-[4-(1-methylcyclohexylmethoxy)benzyl]-thiazolidine-2,4-dione (ADD-3878, U-63, 287, ciglitazone), a new antidiabetic agent. *Diabetes* 32:804–10, 1983
7. Kawazu S, Suzuki M, Negishi K, Ishii J, Sando H, Katagiri H, Kanazawa Y, Yamanouchi T, Akanuma Y, Kajinuma H, Suzuki K, Watanabe K, Itho T, Kobayashi T, Kosaka K: Initial phase II clinical studies on midaglizole (DG-5128): a new hypoglycemic agent. *Diabetes* 36:221–26, 1987
8. Tutwiler G, Teuman R, Joseph J, Mihan B, Fawthrop H, Brentzel H: Pharmacologic profile and insulin secretagogue effect of linogliride (McN-3935), a new orally effective hypoglycemic agent. *Drug Dev Res* 9:273–92, 1986
9. Colca JR, Morton DR: Antihyperglycaemic thiazolidinediones: ciglitazone and its analogues. In *New Antidiabetic Drugs*. Bailey CJ, Flatt PR, Eds. London, Smith-Gordon/Nishimura, 1990, p. 255–61
10. Kosaka K, Kuzuya T, Akanuma Y, Hagura R: Increase in insulin response after treatment of overt maturity-onset diabetics is independent of the mode of treatment. *Diabetologia* 18:23–28, 1980

Visceral Afferent Neuropathy in Diabetic Gastroparesis

Wolfgang Rathmann, MD
Paul Enck, PhD
Thomas Frieling, MD
F. Arnold Gries, MD

Objective: To determine whether a lack of symptoms in diabetic patients with gastrointestinal motility disorders is associated with visceral afferent neuropathy. Research Design and Methods: We investigated cerebral evoked potentials (EPs) after esophageal stimulation in 10 patients with motor dysfunction of the gastrointestinal tract and in 10 healthy control subjects. All patients had insulin-dependent diabetes mellitus (5 men, 5 women, age range 31–60 yr, diabetes duration 8–36 yr, 10 of 10 with polyneuropathy, 6 of 10 with cardiac autonomic neuropathy). Their esophageal and gastric motor disorders had been diagnosed by scintigraphy, and gastrointestinal stenosis had been excluded by gastroscopy. Only 2 patients had severe symptoms, whereas 6 patients complained of minor discomfort (distension, bloating), and 2 patients were symptom free. Results: EPs were recorded after electrical stimulation of the esophagus (32 cm from the incisors) at intensity just above the perception threshold. All control subjects exhibited regular EPs at 0.1 ms/30 mA stimulation intensity. In 6 diabetic patients, no EPs were detected at 0.1 and 0.3 ms/30 mA, and the perception thresholds were significantly elevated. In 4 patients with normal perception threshold, EPs of regular shape but decreased amplitude were recorded. These patients had mild or severe gastroparetic complaints. Conclusions: These data show for the first time an association between a lack of symptoms in diabetic gastrointestinal motility disorders and visceral afferent neuropathy.
***Diabetes Care* 14:1086–89, 1991**

Abnormal autonomic nervous system function is a common complication of long-standing diabetes mellitus (1) that frequently may affect the gastrointestinal tract (2). However, a lack of symptoms has been reported in diabetic patients with proven gastrointestinal motility disorders, suggesting that a reduced sensitivity of afferent pathways may be associated with autonomic diabetic neuropathy (3,4). However, specific nerve damage of gastrointestinal afferents in humans has not been subject to diagnostic evaluation because specific research tools were not available. It has been shown that cerebral evoked potentials (EPs) can be recorded after stimulation of the esophagus in healthy subjects (5). This technique provides the opportunity to assess nerve conduction of afferent pathways from the gut to the brain. We applied this technique in the investigation of diabetic patients with proven motor dysfunction of the gut.

RESEARCH DESIGN AND METHODS

Ten patients with insulin-dependent diabetes mellitus (IDDM) were studied. These included five men and five women with an age range of 31–60 yr and diabetes duration of 8–36 yr. All patients had brittle diabetes. Blood glucose concentration ranged from 5.5 to 10 mM before testing (13). Esophageal and gastric motility dys-

function had been previously diagnosed by scintigraphy (6). Gastrointestinal stenosis as the origin of the motility disorder was excluded by gastroscopy in every patient. Gastric emptying mesurement was performed with a double-isotope test with a solid meal (pancake) containing ^{99m}Tc-labeled nanocolloid and a liquid meal consisting of 250 ml water labeled with ^{113m}In. Delayed gastric emptying of solid meal was defined as values >2SD above the mean of a control group and occurred in all patients. Six patients had irregular minor gastrointestinal symptoms, i.e., bloating and abdominal discomfort, and two patients were symptom free. No patient suffered from dysphagia. Two patients had recurrent severe symptoms, i.e., nausea and vomiting.

Peripheral neuropathy was assessed by standardized investigations (nerve conduction velocity, vibration perception threshold; (1) and was present in all patients. Cardiac autonomic neuropathy was determined by a battery of four tests including beat-to-beat variation at rest and during forced respiration, Valsalva maneuver, and an orthostatic reaction test (1,8). The tests were graded as abnormal in six patients. Ten healthy volunteers (5 men, 5 women, age range 29–50 yr) with no history of chronic gastrointestinal symptoms served as control subjects. Informed written consent was obtained from each proband, and the study was approved by the ethical commitee of the medical school of the Heinrich-Heine-University (Düsseldorf, Germany).

Measurement of EP. Without preparation, other than a 6-h fasting period, the stimulation probe with bipolar Ag/AgCl electrodes was positioned 32 cm from the incisors. Before recording EPs, the individual minimal perception threshold for 1 Hz electrical stimuli in the esophagus was assessed by slowly increasing the stimulus voltage (0–50 mA) at different duration of stimulation (0.1, 0.3, and 1.0 ms) until the subjects felt a pulsing sensation in the thorax. Longer stimulation duration (0.3–0.1 ms) strongly increased the stimulation perception. Three runs were performed at each stimulation frequency to prove reproducibility. In diabetic patients, an upper stimulation limit of 0.3 ms/30 mA was maintained.

Esophageal stimuli were applied at the individual perception threshold (or the upper limit) with a frequency of 1 Hz. Cerebral responses were recorded from the vertex (Cz, international 10–20 system) and the forehead (Fz, reference electrode) after 32 stimuli averaged at a time base of 500 ms. Electrode to skin impedance was <2 kΩ. Amplifier gain was 50 μV/cm, and filter setting ranged from 1 to 100 Hz. Stimulation was performed in two trials at a given stimulus voltage with a control recording without electrical stimulation after disconnecting the probe from the stimulator. A three-lead electrocardiogram (arms and left leg) was performed during the stimulation to detect cardiac arrythmias. The control subjects were instructed to avoid movements of their closed eyes, and any acoustic stimuli were avoided during the recording.

RESULTS

The perception thresholds for electrical stimulation in diabetic patients and control subjects are in Table 1. The perception of rhythmical pulsing sensations could be achieved in all control subjects and depended on stimulus intensity and duration (Table 1). In diabetic patients, perception thresholds were significantly higher than in control subjects. Among patients with almost normal perception (0.1 ms/35 mA), all had gastroparetic complaints. Stimulation >0.3 ms/30 mA was not performed to avoid the induction of cardiac arrhythmias, which occurred in one patient at this level.

EP in response to electrical stimulation could be obtained and reproduced in all control subjects (Fig. 1). The latencies of potentials (N1, N2) are shown in Table 1 and are comparable to previous studies (5). In four diabetic patients with detectable perception threshold, cerebral EP were elicited with latencies within the range of control subjects. Two of the patients with normal perception thresholds and detectable EP suffered from severe gastroparetic symptoms. In six patients with no perception at stimulation of 0.3 ms/30 mA, no EP were detectable (Fig. 2). Two of these patients had a total lack of gastrointestinal complaints.

CONCLUSIONS

It has been shown that cerebral EP can be reliably recorded in response to electrical stimulation of the distal esophagus in healthy subjects (5). This specific technique allows the investigation of visceral afferent pathways from the upper gastrointestinal tract to the brain. It is applied in this study for the evaluation of diabetic patients with proven gastrointestinal motor dysfunction.

The long latencies of cerebral responses observed after both electrical (5) and balloon (7) stimulation of the esophagus implies that the stimulation signal is transferred centrally mainly via afferent fibers of the vagus. However, vagal dysfunction is common in diabetic autonomic cardiac neuropathy (8). It has been suggested that vagal dysfunction may have important influence on gastrointestinal motility in patients with autonomic neuropathy (10,11).

However, long-standing diabetic patients with proven upper gastrointestinal motor dysfunction often lack typical gastroparetic symptoms, i.e., nausea and bloating (2–4). Although prolonged esophageal transit times were found in 11 of 16 patients with cardiac autonomic neuropathy, none of the patients reported dysphagic symptoms (12). This has been attributed to a reduced sensitivity of the gastrointestinal tract to identify motor disturbances because of autonomic neuropathy.

This hypothesis could be substantiated in our study. Although all control subjects exhibited regular EPs at a narrow perception threshold level for electrical stimuli, 7 of 10 patients with upper gastrointestinal motor dys-

TABLE 1
Minimal perception thresholds and latencies of evoked potentials after electrical stimulation of the esophagus

Subject	Age (yr)	Sex	Cardiovascular autonomic neuropathy	Gastrointestinal symptoms	Perception thresholds (ms/mA)	Latencies (ms)	
						N1	N2
Control							
1	50	M		None	0.1/30	65	183
2	36	M		None	0.1/25	98	210
3	35	M		None	0.1/20	110	217
4	32	M		None	0.1/25	73	
5	32	F		None	0.1/25	83	
6	38	F		None	0.1/35	91	189
7	53	M		None	0.1/25	119	232
8	45	F		None	0.1/25	111	180
9	42	F		None	0.1/35	111	180
10	29	F		None	0.1/30	140	199
Mean ± SD	37 ± 6					100 ± 23	205 ± 21
Diabetic							
1	60	M	Present	None	>0.3/30		
2	46	M	None	Minor	>0.3/30		
3	44	M	None	Minor	0.3/30	121	154
4	32	M	Present	Severe	0.1/35	86	242
5	33	F	Present	Minor	>0.3/30		
6	52	F	Present	Minor	>0.3/30		
7	56	M	None	Minor	0.1/35	135	204
8	49	F	None	Severe	0.1/30	112	193
9	41	F	Present	Minor	>0.3/30		
10	31	F	Present	None	>0.3/30		
Mean ± SD	44 ± 11					114 ± 21	198 ± 36

function had increased perception thresholds, and 6 patients had a severe defect in afferent nerve conduction from the gut to the brain. Among 3 patients with almost normal perception and regular EPs, although reduced in amplitude, 2 suffered from severe gastroparetic symptoms, whereas the others had either no or only minor gastrointestinal complaints. Although the number of subjects in our study was small, this observation supports the view that the lack of symptoms in diabetic gastroparesis is due to specific visceral afferent neuropathy. Because visceral afferents are involved in the control of gastrointestinal function, an alteration in afferent thresholds could have significant effects on gastrointestinal motility, contributing to delayed gastric emptying (14).

Our study demonstrates the importance of specific diagnostic tools to assess gastrointestinal autonomic neuropathy in diabetic subjects, but the stimulation

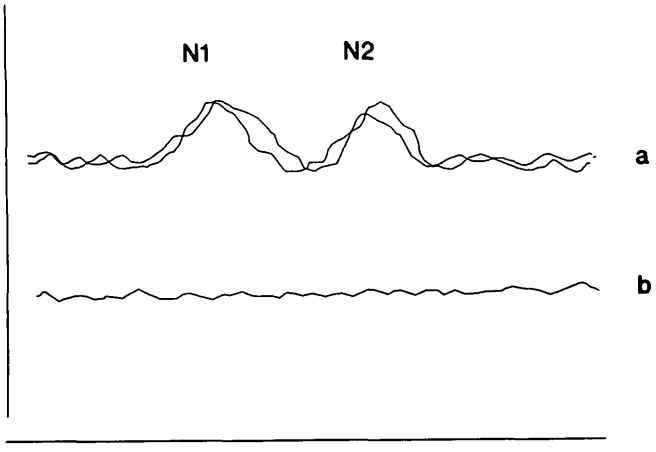

FIG. 1. Evoked potential from control subject. *a*, 2 responses after 32 stimulations each with stimulus duration of 0.1 ms, stimulus voltage 30 mA, and frequency of 1 Hz. *b*, Control recording after disconnection of probe. N1 and N2, latencies of potentials.

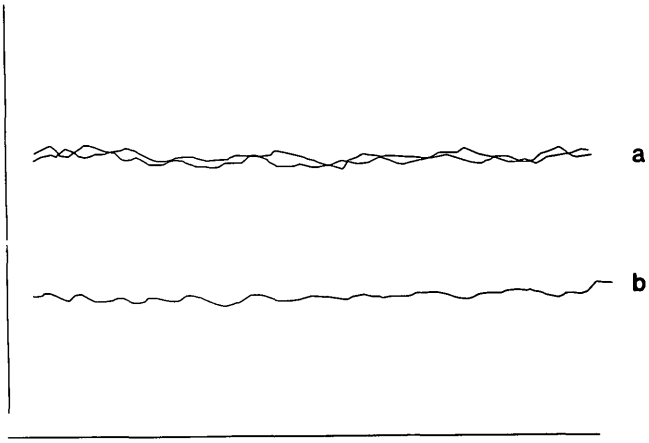

FIG. 2. Evoked potential from diabetic patient (no. 1). *a*, 2 responses after 32 stimulations each with stimulus duration of 0.3 ms and stimulus voltage of 30 mA. *b*, Control recording.

technique we applied is not without risk for these patients. We observed induction of cardiac arrhythmia (single extrasystolic beat) in one patient (no. 5) without known coronary artery disease but decreased beat-to-beat variation. For routine studies, balloon stimulation (7,9), a less-invasive and probably more physiologically stimulating technique, may be more appropriate for the investigation of afferent pathways from the gut to the brain in diabetes mellitus.

From the Diabetes Research Institute, Department of Gastroenterology, Heinrich-Heine University of Düsseldorf, Düsseldorf, Germany.

Address correspondence and reprint requests to Dr. Wolfgang Rathmann, Diabetes Research Institute, Auf'm Hennekamp 65, D-4000 Düsseldorf, Germany.

Received for publication 27 August 1990 and accepted in revised form 10 June 1991.

REFERENCES

1. Ziegler D, Cicmir J, Wiefels K, Berger H, Gries FA: Peripheral and autonomic nerve function in long-term insulin-dependent diabetes. *Diabetes Res* 4:9–14, 1987
2. Buysschaert M, Moulart M, Urbain JL, Pauwels S, deRoy L, Ketelslegers JM, Lambert AE: Impaired gastric emptying in diabetic patients with cardiac autonomic neuropathy. *Diabetes Care* 10:448–52, 1987
3. Clouse RE, Lustman PJ: Gastrointestinal symptoms in diabetic patients: lack of association with neuropathy. *Am J Gastroenterol* 84:868–72, 1989
4. Russel COH, Gannan R, Coatsworth J, Neilsen R, Allen F, Hill LD, Pope CE: Relationship among esophageal dysfunction, diabetic gastroenteropathy, and peripheral neuropathy. *Dig Dis Sci* 28:289–93, 1983
5. Frieling T, Enck P, Wienbeck M: Cerebral responses evoked by electrical stimulation of the esophagus in normal subjects. *Gastroenterology* 97:475–78, 1989
6. Keshavarzian A, Iber FL, Vaeth J: Gastric emptying in patients with insulin-requiring diabetes mellitus. *Am J Gastroenterol* 82:29–35, 1987
7. Castell DO, Wood JD, Frieling T, Wright FS, Vieth RF: Cerebral electric potentials evoked by balloon distension of the human esophagus. *Gastroenterology* 98:662–66, 1990
8. Ewing DJ, Clarke BF: Diagnosis and treatment of diabetic autonomic neuropathy. *Br Med J* 285:16–18, 1982
9. Smout AJPM, DeVore MS, Castell DO: Cerebral potentials evoked by esophageal distension in humans. *Am J Physiol* 259:G955–59, 1990
10. Feldman M, Schiller LR: Disorders of gastrointestinal motility associated with diabetes mellitus. *Ann Intern Med* 98:378–84, 1983
11. Channer KS, Jackson PC, O'Brien J, Corrall RJM, Coles DR, Davies ER, Virjee JP: Oesophageal function in diabetes mellitus and its association with autonomic neuropathy. *Diabetic Med* 2:378–82, 1985
12. Vannini P, Ciavarella A, Corbelli C, Mustacchio A, Cuppini P, Forlani G, Monetti M: Oesophageal transit time and cardiovascular autonomic neuropathy in type 1 (insulin-dependent) diabetes mellitus. *Diabetes Res* 11:21–25, 1989
13. Fraser RJ, Horowitz M, Maddox AF, Harding PE, Chatterton BE, Deut J: Hyperglycaemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 33:675–80, 1990
14. Mayer EA, Raybould HE: Role of visceral afferent mechanism in functional bowel disorders. *Gastroenterology* 99:1688–704, 1990

Effect of Antihypertensive Drugs on Insulin Absorption

Jan Veenstra, MD
Jan P. van der Hulst, MD
Ingrid H. Wildenborg, MD
Suzy F. Njoo, MD
Wim P. Verdegaal, MD
Joseph Silberbusch, MD

Objective: To examine the effects of antihypertensive drugs on the absorption of subcutaneously injected insulin. Research Design and Methods: Eleven healthy volunteers (group 1) were given 1 mg/kg body wt propranolol three times a day during 48 h and a single dose on the morning of investigation. Seven other healthy volunteers (group 2) were given 10 mg nifedipine 30 min before subcutaneous injection of 10 U ^{125}I-labeled soluble insulin. Absorption was measured by counting radioactivity externally. In both groups, control experiments were conducted under the same conditions without administration of propranolol or nifedipine. Results: Propranolol usage was associated with higher mean percentages of remaining activity ($P < 0.05$ by analysis of variance [ANOVA]) than in the control experiment. In the nifedipine experiment, mean percentages were significantly lower compared with the control experiment ($P < 0.02$ by ANOVA). The mean decline in activity of all 30-min periods was 6.8 ± 3.5 vs. 3.6 ± 3.7% for control versus propranolol (group 1) ($P < 0.05$) and 6.3 ± 1.8 vs. 9.6 ± 3.2% for control versus nifedipine (group 2) (NS). Conclusions: Antihypertensive drugs can influence insulin absorption. Propranolol (a peripheral vasoconstrictor) decreases insulin absorption, whereas nifedipine (a vasodilatator) increases insulin absorption. *Diabetes Care* 14:1089–92, 1991

Many factors influence the absorption of insulin. These factors have been grouped according to insulin preparation (i.e., concentration, volume, dose, species), method of administration (i.e., injection technique, mixing of insulins),