Plasma Norepinephrine in Sensory Diabetic Polyneuropathy

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OBJECTIVE— To examine whether changes in circulating norepinephrine are associated with the sensory disturbances of diabetic polyneuropathy. Experimental studies have indicated that NE can excite sprouts from injured nerves, producing pain.

RESEARCH DESIGN AND METHODS— We measured supine and erect plasma NE in 13 normal, nondiabetic control subjects and three groups of diabetic patients: 20 without clinical neuropathy, 20 with chronic painful neuropathy, and 15 with painless neuropathy and foot ulceration. Neuropathy was characterized by symptom and deficit scores, sensory thresholds, electrophysiology, and cardiovascular autonomic function tests. Neuropathic pain was scored by the patients on a linear analogue scale.

RESULTS— In painless neuropathy, NE levels were greatly reduced (supine, 1.3 nM; erect, 2.2 nM) compared with control subjects (supine, 2.4 nM; erect, 4.0 nM; $P < 0.001$) and were combined with grossly abnormal autonomic reflexes. NE also was reduced in the diabetic group without neuropathy (supine, 1.7 nM; erect, 2.7 nM; $P < 0.01$ vs. control subjects). By contrast, in painful neuropathy NE levels (supine, 2.2 nM; erect, 3.6 nM) were similar to control subjects and significantly higher than in painless neuropathy ($P < 0.01$). Furthermore, NE correlated with the severity of neuropathic pain ($r = 0.46$, $P = 0.02$). To assess whether pain, acting as a stressor, could account for the observed differences in NE, we also measured the stress hormones epinephrine and cortisol. They did not differ among the diabetic groups.

CONCLUSIONS— Circulating NE is higher in painful than painless diabetic neuropathy. We suggest that painful neuropathy is associated with a relatively higher number of functioning sympathetic fibers that may contribute to pain.

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NE, NOREPINEPHRINE; CCR, CREATININE CLEARANCE; SBP, SYSTOLIC BLOOD PRESSURE; EPI, EPINEPHRINE; HPLC, HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY; CV, COEFFICIENT OF VARIATION; RIA, RADIOIMMUNOASSAY; ANOVA, ANALYSIS OF VARIANCE; BMI, BODY MASS INDEX; IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS.

The cause of pain in diabetic neuropathy remains uncertain (1). Overexcitability and aberrant firing from regenerating afferent neurons is widely held to be responsible (2,3). Yet, neuronal sprouting appears to occur equally in patients with painful and painless diabetic polyneuropathy (4), suggesting that other factors, local or systemic, may interfere with painful impulse generation and/or transmission.

Previous studies have implicated activation of the sympathetic nervous system in the pathogenesis of many neuropathic pain syndromes (5,6). The burning pain and dysesthesia described in diabetic neuropathy are remarkably similar in character to those in patients in whom sympathetic blocks relieve pain. Furthermore, evidence indicates noradrenergic manipulations may be clinically useful; studies have reported, for example, the α_2-adrenergic agonist clonidine (8) and the selective NE reuptake blocker desipramine (9,10) relieve neuropathic pain in some diabetic patients.

Our study, therefore, examined whether differences in sympathetic nerve activity between the syndromes of sensory diabetic polyneuropathy might help explain the different patterns of sensory disturbances observed. Distinct examples of this clinical diversity are the syndromes of chronic painful neuropathy and severe painless neuropathy with foot ulceration. Notably, differences in the degree of autonomic reflex dysfunction have been described between these two clinical syndromes (11,12). Reflex abnormalities, however, may not parallel the level of prevailing sympathetic activity, because they test composite sympathetic function in response to a defined physiological stimulus (13). In contrast, plasma NE is a reflection of ongoing peripheral sympathetic nerve firing, representing NE that spills over into the circulation after its release from postganglionic sympathetic neurons (14).

We investigated the question of

sympathetic involvement in the sensory disturbances of diabetic polyneuropathy by measuring circulating NE and by examining whether it relates to the presence or severity of neuropathic pain.

RESEARCH DESIGN AND METHODS

— We studied 13 nondiabetic control subjects, 20 diabetic patients with no clinically detectable somatic or autonomic neuropathy, 20 diabetic patients with painful neuropathy of >1-yr duration, and 15 diabetic patients with painless neuropathy associated with recurrent foot ulceration. None of the patients with painless neuropathy could recall any positive symptoms of neuropathy. The district ethics committee approved the study, and all participants gave their informed consent.

The presence of diabetic retinopathy was assessed with standard seven-field color retinal photography (15). For the purpose of analysis, it was characterized simply as nonvisually threatening (background) and visually threatening (preproliferative, proliferative, or maculopathy). Proteinuria was quantified on 24-h urine collections, and renal function was assessed by serum creatinine and CCr. All patients had normal CCr, proteinuria <1 g/24 h, normal erythrocyte mean corpuscular volume, liver and thyroid function tests, and an ankle/branchial sBP ratio >1. None was in heart failure.

All patients were questioned about symptoms of autonomic neuropathy: sweating disturbance, postural hypotension, genitourinary abnormality, and gastrointestinal symptoms. To obtain a neurological deficit score, we performed a standard evaluation of the peripheral nervous system, comprising assessment of light touch (cotton-wool), vibration (tuning fork 128 cps), pain (pin prick), temperature (cold metal), and tendon reflexes, as described previously (16). Peroneal and sural nerve-conduction studies were performed with standard surface-stimulating and recording electrodes in the right leg.

Four tests of cardiovascular autonomic function were used (16): the maximum-minimum heart rate (beats/min), the heart-rate response to Valsalva maneuver, the heart-rate response to standing from lying (30:15 ratio), and the change in sBP in response to standing from a supine position. Vibratory thresholds were calculated as the mean of three measurements on the first left metatarsal bone using a Biothesiometer (Bio Medical Instruments, OH). Cutaneous thermal thresholds were assessed on the sole of the left foot by a Middlesex computer-assisted thermostimulator (17).

The patients themselves scored the severity of neuropathic pain at the time of the study with a linear numeric pain scale from 0–10. All medication for the relief of neuropathic pain, including tricyclics and β-adrenergic blockers had been discontinued for at least 4 days.

Patients were admitted early in the afternoon. After the insertion of an antecubital vein catheter, they were allowed to rest supine in a controlled, quiet environment. Blood for catecholamine measurement was obtained at 1700 after at least 45 min of rest in the supine position, and then 5 min after standing up. Samples were collected in heparinized tubes, immediately centrifuged and stored at −70°C until assayed. All patients took their usual dose of insulin or hypoglycemic tablets before breakfast, and ate breakfast and lunch. None drank coffee, smoked, ate, or injected insulin within 3 h before sampling, and all were well hydrated. Blood glucose was monitored during the study to exclude hypoglycemia.

Plasma NE and EPI were measured with HPLC with reversed-phase ion-pair chromatography and electrochemical detection (18). The detection limit for both EPI and NE was 0.1 nM. The CV was <10% between assay and <5% within assay for both EPI and NE. RIA measured plasma cortisol, with sensitivity of 56 nM and between and within assay CV of <10%.

A one-way ANOVA tested for overall group differences. Differences between pairs of groups were assessed with a Mann-Whitney two-sample test, and differences between supine and erect NE levels were tested by Wilcoxon's signed-rank test. Data derived from neurophysiological assessment were tested for interdependence between them and with plasma catecholamine data by Spearman's rank correlation analysis.

RESULTS

Clinical and neurophysiological measurements

No overall differences existed betweem the groups in age, BMI, duration of diabetes, or glycemic control (HbA_1) (Table 1). Symptoms of autonomic neuropathy were more frequent in the patients with painless foot ulceration (14 of 15 patients) versus those with painful neuropathy (13 of 20 patients). Retinopathy (background and visually threatening) and proteinuria also were more common in the diabetic patients with painless neuropathy. Renal function tests, however, were comparable in the groups.

The diabetic group without neuropathy had cardiovascular autonomic function comparable to the nondiabetic control group, but slight impairment of electrophysiology and elevation of sensory thresholds (Table 2). In both neuropathic diabetic groups, nerve-conduction studies, sensory thresholds, and cardiovascular autonomic function were clearly abnormal, but were significantly worse in the patients with painless neuropathy.

When considered individually, the patients with painless neuropathy had almost invariable impairment of all neuropathy parameters tested. In contrast, the patients with painful neuropathy showed a wide range of nerve conduction and cardiac autonomic reflex abnormalities (from normal to clearly abnormal). The postural drop in blood pressure varied in both neuropathic groups, and no significant numerical differences existed between them. Postural

Table 1—*Clinical characteristics of diabetic patients and control subjects*

	Control subjects	Diabetic patients		
		No neuropathy	Painful neuropathy	Painless foot ulceration
n (M/F)	8/5	14/6	12/8	11/4
Age (yr)	50 (27–63)	51 (25–64)	48 (25–65)	51 (30–65)
BMI (kg/m^2)	27 (22–31)	27 (20–32)	26 (20–34)	28 (20–40)
Duration of diabetes (yr)		10 (2–22)	13 (2–25)	14 (5–30)
IDDM/NIDDM		8/12	9/11	6/9
HbA_1 (%)		9.3 (7.5–14.0)	9.6 (6.9–12.9)	10.2 (7.4–12.3)
Serum creatinine (μM)	82 (67–114)	88 (66–120)	82 (64–110)	94 (68–129)
Proteinuria (300–1000 mg/24 h)	0	7	10	11
Retinopathy				
Background		8	11	11
Visually threatening			2	4
Autonomic symptoms				
Sweating disturbances			12	11
Postural hypotension			8	9
Genitourinary abnormality			15	12
Gastrointestinal symptoms			7	6
Neuropathy deficit score	0	0 (0–1)	14 (2–23)*	20 (10–26)†

Data are means (ranges).
*$P < 0.001$ vs. no neuropathy.
†$P < 0.01$ vs. painful neuropathy.

hypotension (<20 mmHg systolic), however, was proportionately more common in painless neuropathy (11 of 15 patients) than in painful neuropathy (9 of 20 patients). All clinical and neurophysiological deficits were intercorrelated ($r = 0.37–0.81$, $P < 0.01–0.001$).

Plasma NE

Basal (supine) plasma NE levels strongly correlated with NE levels after postural stimulation (erect) ($r = 0.91$, $P < 0.001$). In the diabetic group without neuropathy, the plasma NE levels (means ± SD) of 1.7 ± 0.6 nM for supine and 2.9 ± 0.8 nM for erect were lower than the levels in normal control subjects, which were 2.4 ± 0.5 nM for supine and 4.0 ± 1.0 nM for erect ($P < 0.01$). This applied equally to IDDM and NIDDM patients (Fig. 1). Therefore, they were grouped together for the rest of the analysis.

In patients with painful neuropathy, supine and erect NE levels were higher (2.2 ± 0.9 and 3.6 ± 1.5 nM, respectively) than in patients with painless neuropathy (supine, 1.3 ± 0.4 nM; erect, 2.2 ± 0.6 nM; $P < 0.05$). They did not differ, however, from the levels in normal control subjects or from those in the nonneuropathic diabetic patients (Fig. 2). Similarly, the mean rise in NE was higher in painful neuropathy (1.4 ± 0.6 nM) than in painless neuropathy (0.9 ± 0.4 nM, $P < 0.05$), remaining comparable to the NE rise in the group with no neuropathy (1.2 ± 0.5 nM) and in normal control subjects (1.6 ± 0.6 nM), as shown in Fig. 3. The increase of NE with posture was significant in all the groups ($P < 0.01–0.001$).

Overall, NE levels did not correlate with the degree of postural hypotension or the degree of cardiac autonomic reflex dysfunction. In the patients with painful neuropathy, however, NE correlated positively with the severity of neuropathic pain, as measured on a linear analogue scale (supine, $r = 0.44$, $P = 0.03$; erect, $r = 0.48$, $P = 0.02$; incremental, $r = 0.46$, $P = 0.02$), as shown in Fig. 4. Plasma EPI levels did not differ significantly between the groups and did not exceed 0.5 nM in the supine position and 0.7 nM in the erect position in the patients with painful neuropathy. Plasma cortisol also was comparable among the three diabetic groups: mean ± SD values were 232 ± 57 nM in the painful neuropathy group; 215 ± nM in the painless neuropathy group; and 190 ± 93 nM in the group with no neuropathy.

CONCLUSIONS — This study shows basal and posturally stimulated plasma NE is higher in diabetic patients with painful neuropathy, compared with those with severe painless neuropathy and foot ulceration. The simultaneous measurement of the stress hormones EPI and cortisol, which, unlike NE, do not differ among the groups, argues against the possibility that pain acting as a stress stimulus could account for our findings. Furthermore, the careful matching of the patients for age and renal function, the exclusion of hypoglycemia during the study, and the discontinuation of tricyclic agents and β-blockers has minimized potential interference of these factors with the NE release or clearance (19).

On the other hand, because of the typical generalized and symmetrical nature of peripheral nerve damage in diabetic polyneuropathy (20), we believe that, although regional variation in NE release does occur (21), the differences in forearm circulating NE among the groups reflect analogous changes in the lower limb and total peripheral sympathetic nerve activity.

We therefore suggest the higher circulating NE levels in painful, compared with painless, diabetic neuropathy reflect the activity of a larger sympathetic nerve-fiber population in the former syndrome. This suggestion is corroborated by the higher incremental NE response to posture in the painful group com-

Table 2—*Sensory thresholds, peripheral nerve electrophysiology, and cardiovascular autonomic function tests*

	Control subjects	Diabetic patients: No neuropathy	Diabetic patients: Painful neuropathy	Diabetic patients: Painless foot ulceration
n	13	20	20	14
Vibratory threshold (volts)	11 ± 4	17 ± 7*	34 (8–>50)†	>50 (38–>50)‡
Cooling threshold (°C)	0.2 ± 0.1	0.5 ± 0.5*	2.9 (0.6–>6.0)†	>6.0 (3.9–>6.0)‡
Warming threshold (°C)	0.7 ± 0.6	2.4 ± 2.3*	>6.0 (3.0–>6.0)†	>6.0 (>6.0)†
Sural sensory conduction velocity (m/s)	37 ± 3	34 ± 4*	28 (20–38)†	20 (20–30)‡
Sural sensory potential amplitude (μV)	11 ± 7.3	6.1 ± 4.2*	2.1 (0–11)†	0 (0–0.5)‡
Peroneal motor conduction velocity (m/s)	48 ± 3	43 ± 4*	38 ± 5†	30 ± 5‡
Maximum-minimum heart rate (beats/min)	20 ± 6	17 ± 8	8 (0–39)†	0 (0–6)‡
Valsalva ratio	1.68 ± 0.27	1.47 ± 0.24	1.33 ± 0.21	1.22 ± 0.18†
30:15 ratio	1.25 ± 0.14	1.19 ± 0.13	1.04 (1.00–1.20)†	1.01 (1.00–1.08)‡
Postural change in BP (mmHg)	4 ± 4	5 ± 6	15 ± 16†	26 ± 15†

Data are means ± SD or medians (ranges). Sural sensory conduction velocity if absent assigned as 20 m/s; vibratory and thermal thresholds when >50 volts and >6°C were assigned values of 60 volts and 7°C, respectively.
*$P < 0.01$ (or better) vs. control subjects.
†$P < 0.01$ (or better) vs. no neuropathy and control subjects.
‡$P < 0.01$ (or better) vs. painful neuropathy, no neuropathy, and control subjects.

pared with the painless group. It also is consistent with the invariably severe autonomic reflex dysfunction observed in the group with painless neuropathy as opposed to the less marked and variable reflex abnormalities in patients with painful neuropathy.

Morphologically, distinguishing autonomic from other types of small nerve fibers is difficult, so no specific pathological data exist. Our suggestion, however, agrees with evidence that the majority of diabetic patients with painful neuropathy, unlike those with painless foot ulceration, retain the ability to constrict peripheral blood vessels in response to sympathetic arousal stimuli (22) and have normal or borderline sweat-spot test scores in the foot (11).

Previous studies of circulating NE in diabetic neuropathy selected patients according to the presence or absence of autonomic symptoms and signs. In a series of 100 nonketotic diabetic patients, Cryer et al. (23) showed mean basal and posturally stimulated plasma NE was normal, but subsets of neuropathic patients were identified as having exaggerated or reduced sympathoadrenal re-

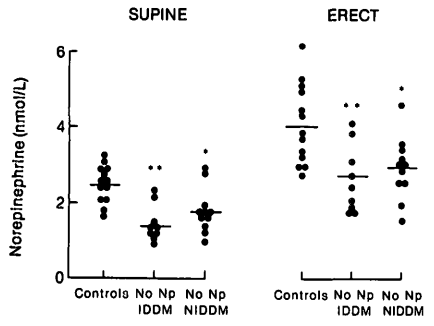

Figure 1—*Basal (supine) and posturally stimulated (erect) plasma NE in IDDM and NIDDM patients without clinical neuropathy. Horizontal bars are the means. (Np), neuropathy. * $P < 0.05$ vs. control subjects. ** $P < 0.01$ vs. control subjects.*

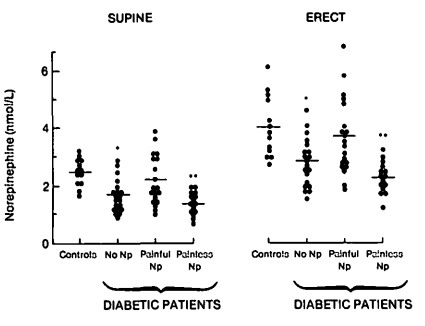

Figure 2—*Plasma NE (supine and erect) in painful and painless neuropathy, comparison with normal and diabetic control subjects. Horizontal bars are the means. (Np), neuropathy. * $P < 0.01$ vs. control subjects; ** $P < 0.01$ vs. control subjects, and $P < 0.05$ vs. painful Np.*

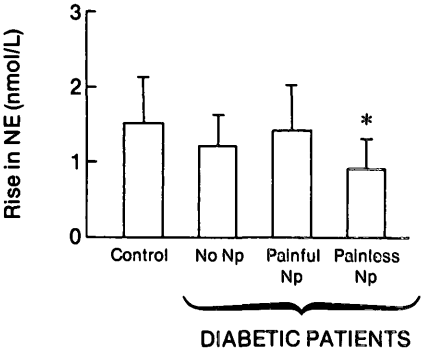

Figure 3—*Postural rise of NE in diabetic patients and control subjects. Levels are the means, and vertical bars are SD. (Np), neuropathy. * $P < 0.05$ vs. painful Np and control subjects.*

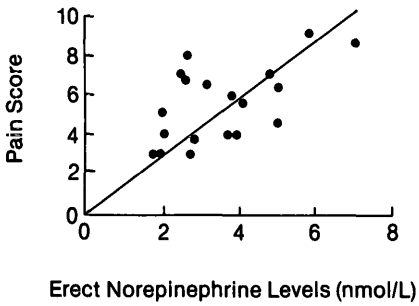

Figure 4—*Correlation of erect plasma NE with the severity of neuropathic pain. The severity of pain was assessed by a linear numerical scale (0-10 cm) and correlated significantly with erect NE ($r = 0.48$, $P = 0.02$) as it did with the supine NE levels ($r = 0.44$, $P < 0.03$) and the incremental NE response to posture ($r = 0.46$, $P < 0.02$).*

sponses. Caviezel et al. (24) found basal and posturally stimulated NE to be reduced in diabetic patients who had autonomic and painless somatic neuropathy. Christensen (25) found plasma catecholamines to be reduced in diabetic patients with peripheral neuropathy in one study, whereas in another study he found no difference in plasma NE between neuropathic and nonneuropathic diabetic patients (26). Other studies showed plasma NE appearance and production rates to be reduced in diabetic patients with autonomic and painless somatic neuropathy (27,28).

In patients without clinical neuropathy, the finding of low basal and posturally stimulated plasma NE levels probably indicates the presence of early sympathetic defects, which are not detected by conventional cardiovascular autonomic function tests. This finding is compatible with the clear evidence of early somatic neuropathy in this group, which, together with a longer duration of diabetes, distinguishes our nonneuropathic group from those found by Caviesel et al. (24) and Christensen (25) to have normal plasma NE. Other studies using dark-adapted pupillary diameter in diabetic children (29) or sweat spots and vascular autoregulation (30) in adults also suggested that sympathetic neuropathy can occur when cardiovascular autonomic reflexes still are normal.

In painful neuropathy, despite the presence of cardiovascular reflex abnormalities, NE levels do not differ significantly from either of the control groups, raising the possibility of a mechanism whereby firing from some functioning sympathetic fibers is increased in this syndrome. We provide evidence that pain itself or other causes of stress are unlikely to cause the higher NE levels in painful neuropathy.

Alternatively, because of the evidence that degenerating and regenerating axons acquire chemosensitivity to catecholamines because of de novo expression of ectopic α-adrenergic receptors on their membranes (31,32,33), we could speculate that higher prevailing NE levels may trigger and/or amplify painful discharge from regenerating fibers. A positive feed-forward circuit, in fact, may be established, whereby the stimulated afferent barrage from overexcitable regenerating C-fibers causes central sensitization of the dorsal horn neurons (34), stimulating sympathetic outflow (34,35), which further increases afferent discharge (2,31,33).

Such a mechanism could explain not only the inappropriately near-normal NE levels in these patients, but also the apparent association of plasma NE with the severity of neuropathic pain. The mechanism also would be compatible with evidence from double-blind, placebo-controlled clinical trials that the selective NE uptake blocker desipramine, which has been shown to reduce central sympathetic outflow (36), and the α_2-adrenergic blocker clonidine are effective in relieving neuropathic pain in subsets of diabetic patients (8,10). In painless diabetic neuropathy with foot ulceration, the more severe axonal loss (4) allied to the gross sympathetic denervation may significantly diminish painful discharge from peripheral nerves.

In summary, we provide evidence that diabetic patients with painful neuropathy have higher circulating NE levels compared with patients with painless neuropathy and foot ulceration, suggesting a higher number of functioning sympathetic fibers in the former. Given the potential of sympathetic fibers to facilitate pain transmission, these results suggest clinical trials of sympathetic blockade might be of interest in painful diabetic neuropathy.

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