Pai n Perception in Patients with Eating Disorders

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The heat pain threshold was measured with phasic and tonic stimuli under basal conditions and after naloxone administration in 10 anorectic and 10 bulimic patients as well as in 11 healthy control subjects. Under both kinds of stimulation, the basal threshold values were elevated in the bulimic patients and in some of the anorectic patients. Naloxone did not differ from placebo in its effect on the pain thresholds (phasic and tonic), suggesting that a nonopioid mechanism was responsible for the threshold elevation found in the eating disorder patients. The plasma cortisol concentration was similar in the three groups and not correlated with the basal pain thresholds in the patients. Other indicators of dieting such as β-hydroxybutric acid and triiodothyronine also showed no correlation with the basal pain thresholds. Significant height correlations can be interpreted as weak evidence that neuropathy is the cause of the increase in the pain threshold.

INTRODUCTION

A disturbed awareness of the bodily state including the perception of proprioceptive and interoceptive stimuli was already considered by Bruch (1) to be an important feature of anorexia nervosa. In subsequent studies a distortion of body image was demonstrated in patients with anorexia and bulimia nervosa. The question remains, however, of whether this disturbance is caused by perceptual, cognitive, or affective variables (2, 3). For the adjustment of the body image, somatosensory stimuli seem to be as important as visual stimuli. Nevertheless, somatosensory perception in patients with eating disorders has been studied only rarely up to now. In a small number of experiments Florin and coworkers found reduced tactile perception in bulimic patients and discussed this finding as a possible contribution to the body image distortion of their patients (4, 5). Their anorectic patients did not show this deficit, but these subjects were only slightly underweight when studied (at the end of therapy).

Pain perception and pain memory have a somatotopic organization as has become evident by clinical research on nerve injuries, the outstanding example being the phantom limb (6, 7). This organization can be strongly influenced by reducing and enhancing the nociceptive input from special body areas (8). These observations have given clear evidence that a highly dynamic "pain body image" exists, which seems to contribute to the formation of the general body image. Therefore distortions of the former produced by changes in pain perception may result in distortions in the latter.

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Another reason for studying the perception of nociceptive stimuli in patients with eating disorders is the altered opioid activity seen in these patients. In the considerable number of studies conducted in the past, mainly the β-endorphin plasma level has been assessed. However, the results have been inconsistent, with increased, unchanged, and decreased levels reported for both anorexia and bulimia nervosa (9–15). Because the influence of systemic β-endorphin on pain perception is far from clear (16), these contradictory findings do not provide a solid basis for making predictions about pain perception in patients with eating disorders. More useful in this context is the observation that patients with anorexia nervosa have increased CSF opioid activity (17). Despite this finding, to our knowledge pain perception in eating disorder patients and its relation to opioid activity has been investigated in only one single case study: Abraham and Joseph (18) reported an increase in pain tolerance after vomiting in a bulimic patient, which was accompanied by an increase in plasma cortisol, a putative marker of systemic β-endorphin. After naloxone administration the pain tolerance level returned to normal.

These considerations and findings point to a disturbed somatosensory and, especially, pain perception in eating disorder patients as a possible contribution to the distorted body image. They also suggest that a systematic investigation of pain perception in such patients would be useful. Based on the assumption that an increase in opioid activity is responsible for the perceptual deficit, we studied pain perception in anorectic and bulimic patients under basal conditions and after administration of naloxone. To determine the effect of β-endorphin in this context, we measured its putative marker, plasma cortisol. Furthermore, we examined the relation between pain perception and eating behavior based on assessments of metabolic and endocrine indicators of dieting (β-hydroxybutric acid, triiodothyronine) (19).

METHOD

Subjects

The subjects were 10 patients with anorexia nervosa, 10 patients with bulimia nervosa, and 11 healthy controls (all females). The diagnosis of the eating disorder was made according to the DSM-III-R criteria (20) with the aid of the SCID (21). Subjects were excluded from the study if they had been on medication for any length of time, with the exception of contraceptives. Other exclusion criteria were the intake of psychoactive drugs in the previous 6 months, alcohol dependency, or clinical evidence of disk disease, neuropathy, hypertension, or dermatosis at the point of pain stimulation. Table 1 shows that the age distribution was similar in all three groups of subjects and that the two patient groups did not differ in duration of illness. The anorectic patients were not only severely underweight but were also shorter than the bulimic patients and the controls. Seven of the anorectic patients controlled their weight only by fasting and three also by occasional vomiting. Seven of the bulimic patients had a history of anorexia nervosa, and three of the anorectic patients had had bulimic episodes. In the bulimia group the number of binges ranged from 4 to 28 per week.

Of the 20 patients participating, 18 were studied at the beginning of inpatient behavior therapy. The other two were in outpatient behavior therapy and still had bulimic symptoms at the time of investigation. No patient received drug treatment during the study or in the course of therapy. To control for menstrual variations in pain sensitivity and opioid activity (22, 23), the control subjects were studied only during the first 14 days of their menstrual cycle. This type of control was impossible in the patients because of oligomenorrhea or amenorrhea.

The protocol was approved by an ethics commission; all subjects gave written informed consent.

Apparatus and Procedure

The subjects were investigated twice, on two different days, at a maximum interval of 5 days. With the exception of drug administration, the procedure was identical on both days. Sessions started at 7:30 a.m. with collection of a blood sample. After 30 minutes pain thresholds were assessed for the first time. The duration of pain threshold measurement was approximately 20 minutes. Drug administration followed: 100 ml saline either with or without 5 mg naloxone (Narcanti®) intravenously. Pain thresholds were determined for the second time 30 minutes after the administration.

Naloxone and placebo were administered in a double-blind design, with neither the subjects nor the investigator of pain perception knowing which treatment was being used. To control for order effects, the active drug and placebo were equally distributed on days 1 and 2. For this purpose the order of naloxone and placebo was randomized for the first half of the subjects in each group and then the second half were treated in the reverse order.

Pain thresholds were assessed with heat stimuli according to two methods, allowing pain perception to be studied under both phasic and tonic stimulation. (Phasic pain stimuli produce only very brief nociceptive stimulation, whereas tonic pain stimuli lead to nociceptive stimulation of a duration long enough to trigger temporal summation processes in pain perception. These processes, and not only pain intensity at the beginning of stimulation, are known to be reduced by opiates (24) and may therefore also reflect the effect of endogenous opioids.) Phasic and tonic pain thresholds were measured with the help of the programs SCHMERZ 1 and SCHMERZ 2, which are part of the pain and thermal sensitivity diagnosis unit PATH-Tester MPI 100 (Phywe Systeme GmbH). This computer-controlled unit produces thermal stimuli by a Peltier thermode (stimulation area: 6 cm^2; contact pressure: 0.4 N/cm^2). The phasic pain threshold was determined by having the subjects stop a temperature rise of 0.7°C/s starting from 38°C as soon as they felt pain. There were eight trials. The threshold was computed as the mean of the peak temperatures of the last five trials. The tonic pain threshold was measured with a modification of the "method of subjective sensitization" (for details see Refs. 25 and 26). The subjects had to adjust the stimulus to the temperature of their pain threshold with heating and cooling buttons, starting from 38°C. Stimulation was then continued for 35 seconds at the temperature adjusted. Changes in intensity of perception due to temporal summation processes during this interval were measured in a second stimulus adjustment procedure. Six trials of this kind were conducted. The threshold was computed as the mean of both stimulus adjustments of the last five trials. The subjects sat in front of a small table, on which were placed the response panel and the signalling devices. Thermode placement was on the lateral dorsum pedis of the right leg.

Treatment effects on subjective state were assessed on eight horizontal visual analog scales with a length of 10 cm and a verbal descriptor at each end. The scales measured tiredness, headache, dryness of mouth, nausea, physical discomfort, bad mood, sensation of warmth, and drowsiness. The scales were administered before each pain perception measurement.

As heat pain perception, to a small degree, depends on the basal skin temperature (27), and as only the small skin area under the thermode is heated to the preset adaptation temperature, skin temperature near the thermode placement was assessed by a PT100 sensor in three readings during pain threshold assessment.

Triiodothyronine (T3) and plasma cortisol were measured by radioimmunoassay (SERONO, Freiburg) as described earlier (28). Interassay variability was 5.6% at an average concentration of 1.1 ng/ml T3 and 7.0% at an average concentration of 125 μg/l cortisol. β-hydroxybutric acid (β-HBA) was measured according to Williamson and Mellonby (29). Interassay variability was 5.1% at 0.53 μmol/ml.

Due to procedural and technical problems, not all measures could be assessed in all subjects.

Evaluation

Two kinds of analyses of variance (MANOVA), each with a group factor and a repeated measurement factor, were computed to determine (a) group differences (factor "group") and differences between days 1 and 2 (factor "day") in the basal values (before treatment) and (b) group differences (factor "group") and differences between naloxone and saline (factor "treatment") in the effects of treatment. The effects of treatment were calculated as the difference between the measurements before and after treatment. When only two groups were compared, *t* tests were used; the relationship between two variables was determined by calculation of Pearson correlation coefficients.

RESULTS

Group Differences in the Basal Values

For all variables that were assessed on both days, the basal values (values before drug administration) did not differ significantly between days 1 and 2 ($p > 0.05$ for all F tests for the factor "day").

The pain thresholds showed differences between the diagnostic groups (see figure 1). The differences were significant for the phasic pain threshold (factor "group"; df 2,28; $F = 4.41$; $p = 0.022$) and close to significant for the tonic pain threshold (factor "group"; df 2,28; $F = 2.82$; $p = 0.076$). The t tests for the mean thresholds of days 1 and 2 revealed that the bulimic patients had significantly higher thresholds than the controls under both phasic stimulation ($t = 3.37$; $p = 0.003$) and tonic stimulation ($t = 2.46$; $p = 0.024$). No other group comparison (anorexia vs. bulimia, anorexia vs. control) yielded a significant difference. Thresholds more than 2 standard deviations above the mean of the controls were found on one or both days in three anorectic patients and three bulimic patients under phasic stimulation and in one anorectic patient and two bulimic patients under tonic stimulation. Hence, at least some anorectic patients had elevated pain thresholds. Phasic and tonic pain thresholds correlated with $r = 0.80$ ($p < 0.001$) and seemed to measure the same aspect of pain perception under the conditions of this study.

The concentration of plasma cortisol was similar in all three groups (factor "group"; df 2,27; $F = 0.31$; $p = 0.735$), with only slightly elevated levels in the anorectic patients. Figure 2 gives the mean of both days and shows that there was a great within-variance in each group. Furthermore, no significant differences were found for the concentration of β-HBA (factor "group"; df 2,24; $F = 1.43$; $p = 0.260$), mainly because of the great variance within the patient groups (see Table 1). The T3 values, however, differed significantly between groups (factor "group"; df 2,27; $F = 14.09$; $p < 0.001$; see Table 1).

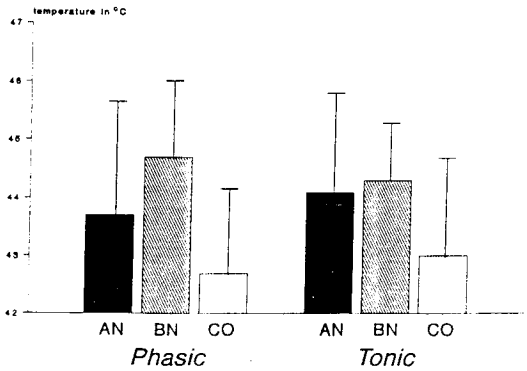

Fig. 1. Mean and standard deviation of the basal pain thresholds (°C) before drug administration (mean of days 1 and 2) for the patients with anorexia nervosa (AN, $N = 10$) and bulimia nervosa (BN, $N = 10$) and for the control subjects (CO, $N = 11$) under phasic and tonic heat pain stimulation.

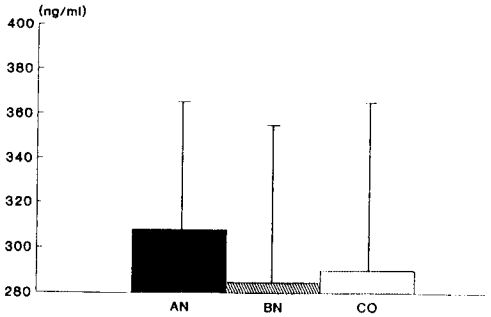

Fig. 2. Mean and standard deviation of the basal plasma cortisol concentration (ng/ml) before pain perception measurement (mean of days 1 and 2) for the patients with anorexia nervosa (AN, $N = 10$) and bulimia nervosa (BN, $N = 9$) and for the control subjects (CO, $N = 11$).

TABLE 1. Anamnestic Data, Body Measures, and Indicators of Dieting (Group Means and Standard Deviations)

	Patient Groups		
	Anorexia nervosa (N = 10)	Bulimia nervosa (N = 10)	Control group (N = 11)
Age (years)	22.7 ± 3.7	22.4 ± 2.9	23.1 ± 3.0
Duration of illness (years)	4.4 ± 2.8	5.2 ± 3.2	
Height (cm)	162.7 ± 4.9	172.8 ± 6.4	170.5 ± 5.4
Weight (kg)	36.8 ± 3.0	60.3 ± 8.9	58.2 ± 2.9
Ideal weight (%)*	66.8 ± 6.0	95.5 ± 12.7	97.9 ± 3.9
β-HBA (μmol/ml)	0.31 ± 0.55	0.17 ± 0.23	0.04 ± 0.06
T3 (ng/ml)	0.94 ± 0.21	1.19 ± 0.28	1.47 ± 0.21
Skin temperature (°C)	27.4 ± 2.2	26.5 ± 1.1	27.0 ± 2.2

* Computed according to the tables of the Metropolitan Life Insurance Company (41).

The anorectic patients had significantly lower T3 values than the bulimic patients ($t = 2.34$; $p = 0.032$) and controls ($t = 5.85$; $p < 0.001$), and the values for the bulimic patients were also significantly lower than those for the controls ($t = 2.53$; $p = 0.021$).

The diagnostic groups did not differ in skin temperature (factor "group"; df 2,28; $F = 0.54$; $p = 0.588$; see Table 1).

Effects of Drug Administration

There was no difference in the effect of naloxone and placebo on the pain threshold under either phasic or tonic stimulation (factor "treatment"; phasic: df 1,28; $F = 2.02$; $p = 0.166$; tonic: df 1,28; $F = 0.69$; $p = 0.413$). The differences between the pain measurements before and after drug administration are given in Figures 3A and B. Moreover, there were no significant group differences (factor "group"; phasic: df 2,28; $F = 0.05$; $p = 0.953$; tonic: df 2,28; $F = 0.88$; $p = 0.427$) or group × treatment interactions ("group" × "treatment"; phasic: df 2,28; $F = 2.45$; $p = 0.105$; tonic: df 2,28; $F = 1.43$; $p = 0.256$). Of the

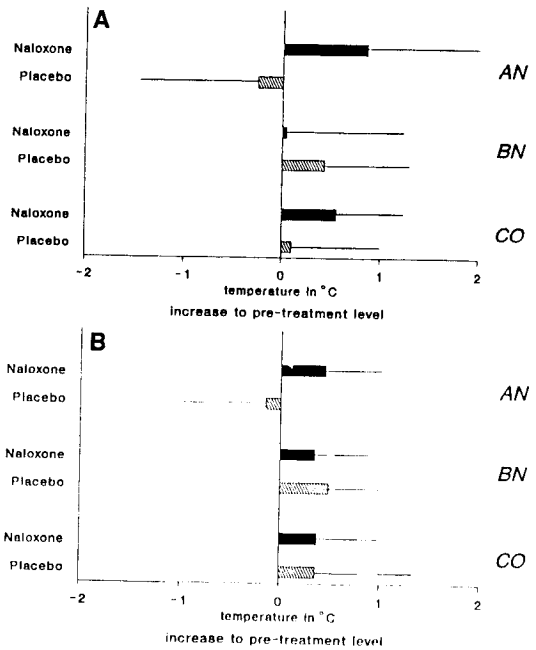

Fig. 3. Mean and standard deviation of the effects of the treatments "naloxone" and "placebo" (mean differences between measurements before and after drug administration) on the pain thresholds (°C) for the patients with anorexia nervosa (AN, N = 10) and bulimia nervosa (BN, N = 10) and for the control subjects (CO, N = 11) under phasic (A) and tonic (B) heat pain stimulation.

eight subjective state scales, only the scale "drowsiness" showed differences between naloxone and placebo (factor "treatment"; df 1,27; $F = 4.86$; $p = 0.036$), with higher values for naloxone.

Correlations of the Pain Thresholds

To find out which variables other than the diagnosis showed covariations with the pain thresholds, we computed correlation coefficients for the correlations between the phasic and tonic pain thresholds and the various basal values (before drug administration) for the combined groups of patients. (As it has been shown in numerous studies that anorexia nervosa and bulimia nervosa are psychopathologically and neurobiologically very closely related disorders, such a combination of the two diagnostic groups is justified for this purpose.) Table 2 shows the results. Only age and height correlated significantly with the pain thresholds. The endocrine and metabolic indicators of dieting, and the plasma cortisol concentration showed no strong relation with the pain thresholds.

TABLE 2. Pearson Correlation Coefficients (r) for the Correlations of the Phasic and Tonic Pain Thresholds with the Anamnestic Data, Body Measures, Endocrine and Metabolic Indicators of Dieting (T3, β-HBA), and Plasma Cortisol for the Two Patient Groups Combined ($N = 20$)

	Pain Threshold (r)	
	Phasic	Tonic
Age	0.36	0.43*
Duration of illness	0.10	0.23
Weight	0.38	0.19
Ideal weight	0.29	0.05
Height	0.41*	0.40*
T3	0.37	0.20
β-HBA	−0.17	−0.10
Plasma cortisol	−0.04	0.17

* $p \leq 0.05$.

DISCUSSION

In the present study an elevation of the pain threshold was found in the bulimic patients and in at least some of the anorectic patients. A further division of the anorectic patients in "only restricters" and "occasional vomiters" did not explain this difference within the anorectic group.

Because the patients showed the known psychobiological indicators of their respective eating disorder, which are specific changes in weight, β-HBA, and T3 (19), this result can be regarded as representative. (As we have earlier demonstrated that hypercortisolism in anorexia nervosa can rapidly reverse after hospital admission (30), the lack of group differences in plasma cortisol levels is rather due to this phenomenon than to a sampling bias.) The differences in pain perception between the patient groups and the control group can hardly be explained by menstrual variations in the latter group because pain sensitivity, if it varies at all, does not seem to be elevated in the first 14 days of the menstrual cycle, the period of investigation in our study (22, 23).

The reduced pain sensitivity in the bulimic and in some anorectic patients is very likely not produced by an increased activity of endogenous opioids: naloxone, an opioid antagonist, did not change the pain thresholds any differently than placebo in either the patients or the controls. These results are similar to those which Stacher and coworkers (31) obtained in healthy subjects using the same dosage of naloxone (5 mg), a similar time pattern of administration, and also heat pain stimu-

lation. The lack of hyperalgesia after the naloxone administration was probably not the consequence of too small a dosage as—especially in the underweight patients—the dosage was sufficiently high to cause antagonistic effects (32), and even in these patients no decrease in pain thresholds was found. Furthermore, some subjects reported an increase in subjective drowsiness, that is, a change in the subjective state, which was found in other studies only when much larger dosages were administered (17, 31).

That the elevation in pain threshold was caused by increased production of pituitary β-endorphin, sometimes found in these patients (10, 11, 13, 14), is also unlikely because no group differences in plasma cortisol concentration were observed. (As ACTH and β-endorphin are produced from the same precursor molecule in the same cell of the anterior pituitary gland and are secreted simultaneously under most physiological conditions, we can assume that cortisol is an indicator of β-endorphin release as it is for ACTH secretion. This parallel secretion of β-endorphin and cortisol has recently confirmed by Young and coworkers (33)). Moreover, the pituitary β-endorphin is more involved in the mechanisms of stress analgesia than in the modulation of pain perception under basal conditions (16).

The observation that phasic and tonic pain stimulation produced similar results suggests that temporal summation processes, which are involved in opiate analgesia (24), were not responsible for the group differences. This is a further argument against the assumption of an opioid mechanism underlying the reduced pain sensitivity in anorexia and bulimia nervosa. Taken together, the results of the present study indicate that pain perception in bulimic and some anorectic patients seems to be reduced by a non-opioid mechanism. This mechanism is different from that described by Abraham and Joseph (18): in a case study of a bulimic patient these authors found an increase in pain tolerance after vomiting that could be reversed by naloxone.

One can speculate that the reduced pain sensitivity is of a neuropathic origin. Manifest forms of peripheral neuropathies have been observed in some patients with eating disorders, but they seem to be restricted to severely ill and long-term patients (34, 35). In anorexia nervosa, MacKenzie and coworkers (35) supposed malnutrition and nerve compression due to the loss of protective tissue to be the causes. However, the unbalanced and restricted nutrition in eating disorder patients might also lead to more subclinical forms of deficiency neuropathies. There is some evidence that the intake of vitamins is reduced and that the intracellular stores of some B vitamins are depleted (36). The lack of B vitamins can cause neuropathies with sensibility dysfunctions (37). Furthermore, drug and alcohol abuse is often found in bulimic patients (38), and this too can produce neuropathic dysfunctions of sensibility. Assuming that a subclinical neuropathy is the mechanism underlying the reduced pain sensitivity, the observed correlation between pain thresholds and height can be explained by the fact that the susceptibility of the peripheral nerves to metabolic or toxic damages depends on their length. Therefore, metabolic and toxic neuropathies typically produce symptoms in a distal-proximal order (39). Consequently, in diabetic neuropathy a relation between neuropathic symptoms and height was found (40). The findings of Florin and coworkers (4, 5) that tactile sensibility as

well is reduced in bulimic patients are compatible with the hypothesis of a neuropathic dysfunction of cutaneous sensibility. This hypothesis needs to be tested in an investigation of further modalities of cutaneous sensibility that are established indicators of specific neuropathic disorders.

The present study demonstrated that reduced pain sensitivity occurs in bulimic patients and in some anorectic patients. Still to be determined is whether this dysfunction leads to an impairment of symptom perception or, as part of a general reduction in somatosensory perception, also contributes to the well-known distortion of the body image.

SUMMARY

Past findings of body image distortions as a possible consequence of disturbed somatosensory processing and of changes in opioid activity in patients with anorexia and bulimia nervosa made an investigation of pain perception in such patients appear useful. We studied heat pain thresholds with phasic (short) and tonic (prolonged) stimuli before and after administration of naloxone and placebo according to a double-blind design in 10 anorectic, 10 bulimic, and 11 control subjects.

Under both kinds of stimulation (phasic and tonic) the bulimic patients and some of the anorectic patients had elevated pain thresholds compared with the control subjects. Naloxone changed the pain thresholds in all subjects in the same way as placebo. The concentration of plasma cortisol, a putative marker of plasma β-endorphin, was similar in the three groups. Neither plasma cortisol concentration nor endocrine indicators of dieting (β-HBA, T3) were correlated with the basal pain thresholds in the patients. The only significant correlations were between height and the two pain thresholds.

The study provided evidence that pain perception is reduced in bulimic patients and in some anorectic patients and that the underlying mechanism is non-opioid. Eating and dieting behavior seems to be of little or no importance for the pain perception changes observed. The greater susceptibility of long afferent pathways to metabolic and toxic damage and the significant height correlations found in the present study suggest neuropathy as the cause of the reduced pain perception.

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