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Effect of naloxone therapy on depersonalization: a pilot study

Yuri L. Nuller, Marina G. Morozova, Olga N. Kushnir and Nikita Hamper

Bekhterev Psychoneurological Research Institute. St-Petersburg, Russia.

To test the hypothesis of the role for the opioid system in the pathogenesis of depersonalization, the effect of naloxone (an opioid receptor blocker) on the symptoms and corticosteroids secretion was studied in patients with depersonalization syndrome. Fourteen depersonalization patients were treated with naloxone: 11 patients received single doses (1.6 or 4 mg i.v.) and three others received multiple infusions, with the maximal dosage being 10 mg, and the effect of naloxone on symptom severity was determined. In eight patients, the cortisol, cortisone and corticosterone content in the blood plasma was determined prior to and after the 4 mg naloxone infusion. A reversed-phase microcolumn high-performance liquid chromatography with ultraviolet detection was applied for assessment of glucocorticoids. In three of 14 patients, depersonalization symptoms disappeared entirely and seven patients showed a marked improvement. The therapeutic effect of naloxone provides evidence for the role of the endogenous opioid system in the pathogenesis of depersonalization.

Key words: depersonalization; glucocorticoids; naloxone

Introduction

Depersonalization is a change of self-awareness such that the person feels unreal. It is characterized by the loss of emotional perception or a blunted feeling of one's own body and its functions, etc. Patients with this condition find it difficult to describe, often speaking of being detached from their own experience and unable to feel emotion. A similar change in relation to the environment is called derealization. Depersonalization can manifest itself as a symptom in the structure of various psychopathological syndromes or as an independent syndrome. In the latter case, where the depersonalization syndrome is unrelated to any other mental disease, it is defined as a depersonalization disorder (Nuller, 1982; American Psychiatry Association, 1994).

Depersonalization syndrome often has a long, lingering course which is resistant to therapy (Shader, 1994). Antidepressants, neuroleptics and electroconvulsive therapy usually fail to produce any therapeutic action. Only very large doses of benzodiazepines produce a therapeutic effect in some patients (Nuller, 1982; Gelder *et al.*, 1989). In cases where depersonalization lasts for months and years, no psychotropic therapy has documented efficacy. When depersonalization is a part of another mental disorder, it is most often a major depression. In such cases, depression can become resistant to therapy and have a lingering course.

An effective medical treatment of depersonalization is impaired by the lack of data on the biochemical mechanisms of this disorder. Depersonalization usually develops as a reaction to severe emotional stress, or can emerge from acute anxiety and tension in various mental illnesses. The fact that anxiety is involved in its genesis is confirmed by the therapeutic efficacy of large doses of anxiolytics in the acute depersonalization syndrome (Nuller, 1982; Nuller and Mickalenko, 1988). Stress can be accompanied by secretion of endogeneous opioids, mostly beta-endorphins. This helps to explain the hypoalgesia or total analgesia found in depersonalization (Nuller and Mikhalenko, 1988; Moroz *et al.*, 1990; Abugova, 1996) as well as a less pronounced pupil reaction to morphine (Nuller and Mikhalenko, 1988). These observations led us to suggest that disturbance in the opioid system such as the increased endorphin secretion and/or a change in the sensitivity of opioid receptors play an important role in the pathogenesis of depersonalization. To verify this hypothesis, we investigated the effect of naloxone – an opioid receptor blocker. Stress is also characterized by changes in secretion of corticoids. Therefore it was of interest to determine the levels of corticoids under depersonalization.

Methods

Subjects

Fourteen patients (nine females and five males, mean age 32 years) were assigned to treatment with naloxone. In six patients, depersonalization was the only manifestation of a mental illness and they met the DSM-IV criteria for depersonalization disorder. Eight patients had mixed depersonalization and depressive symptoms with dominating depersonalization syndrome. In three patients, the duration of the disease was less than 1 year, in seven patients, it ranged from 1–5 years; in two patients, from 5–10 years and in two patients, 14 and 16 years.

The control group for plasma corticosteroids included 36

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healthy volunteers whose age ranged from 25–45 years and whose corticosteroid level in the blood plasma was determined twice for two subsequent days.

Naloxone administration

Naloxone (Polfa) was injected i.v. at 12 in the afternoon in a single-blind placebo controlled design, with placebo always first. The patients had one dose of naloxone, which was followed by further doses if they did not respond. Eleven patients had one infusion, the doses were 4 mg in nine patients and 1.6 mg in two patients. Three patients had multiple naloxone infusion: in one case, 2 mg infusions within 3 days (6 mg total) and, in two other cases, multiple infusions with doses increasing from 2 mg to 10 mg every 2 or 3 weeks (50 mg total). The maximal number of infusions administered was 10. Between the naloxone infusions, these two patients received tranquilizers (lorazepam, 6 mg per day; phenazepam, 8 mg per day; hydroxyzine, 200 mg per day) and antidepressants (paroxetine, 60 mg per day; mianserine, 90 mg per day).

Biochemical methods

The cortisol, cortisone and corticosterone content in the blood plasma was determined in eight patients prior to and after the naloxone infusions. Blood was taken from a catheter inserted into the ulnar vein, and kept open with heparin. The first sample was taken at 11.00 h immediately after the catheter was inserted; the second at 11.30 h, after 10 ml of physiological solution (placebo) was infused iv.; the third at 12.00 h, then the infusion of 0.4 mg of naloxone (1 ml of naloxone solution and 9 ml of the physiological solution) was made; the fourth at 12.15 h before the 4 mg naloxone infusion (10 ml of the solution) and the fifth at 12.30 h.

For measurement of glucocorticoids, a reversed-phase micro-column HPLC with ultraviolet (UV) detection was applied. A 150 × 1 mm column filled with Separon SGX C18 5µ and linear gradient elution (70 : 30 to 35 : 65 water-acetonitrile for 30 min) was used. The technique allowed a good baseline separation of aldosterone, cortisol, cortisone and corticosterone (Gamper *et al.*, 1996). The detection limit (UV detection at 254 nm) was approximately 5 ng/ml. Serum protein electrophoresis was used to extract the substances of interest from the serum.

Results

Efficacy was assessed using the depersonalization scale (Nuller and Mikhalenko, 1988) and subjective response. The depersonalization scale was administered before the naloxone infusion and after 4 h (peak effect). In three of 14 patients, depersonalization symptoms disappeared entirely. Seven patients showed a marked improvement: with symptoms reduced by more than 50% on the depersonalization scale. One patient showed moderate improvement and, in two patients, the improvement was short and insignificant, one patient showed no positive effect.

Thus, 10 of 14 patients showed a considerable therapeutic effect, which is undoubtedly a success considering the therapeutic resistance of the depersonalization syndrome. In addition, the subsequent benzodiazepine therapy (lorazepam, 6 mg per day; phenazepam, 8 mg per day; hydroxyzine, 200 mg per day within 4 weeks) resulted in a fast and complete reduction of depersonalization in three patients (two demonstrated considerable and one moderate improvement), although, in two of these patients, the same drugs were not effective prior to the naloxone therapy.

After reduction of depersonalization, four patients showed no evidence of any mental disorder except for the personality traits they had had in the premorbid period; five patients continued to express the symptoms of major depressive disorder, which was less severe than before the depersonalization had manifested itself and responded quickly to the antidepressants; one patient was found to be deluded with intense anxiety. This condition showed a good response to antipsychotic therapy.

In most cases, the first signs of improvement were recorded soon after the naloxone infusions (within 20–40 min) and the patients' perception of the world was marked by greater brightness. A complete reduction or disappearance of depersonalization occurred within the interval of 1–4 h and, in some patients, continued for as long as 12–24 h. This was followed by some deterioration, although the depersonalization never recurred to the initial level. Five patients showed evidence of a stable improvement.

Two patients had considerable but not total reduction of depersonalization due to the naloxone therapy. Immediately thereafter, they received long-term benzodiazepine treatment. The impression was that benzodiazepines stabilize the improvement that was reached as a result of the naloxone therapy.

No side-effects were recorded when naloxone was administered.

Table 1 presents the corticosteroid data. The depersonalization patients have a very low initial cortisol level compared to the control. The cortisone level also decreased, but to a smaller degree, whereas the corticosterone content appeared to be slightly higher. Upon 4 mg naloxone infusion, the cortisol content was found to reliably increase compared to its post-placebo level. With respect to cortisone, it increased but not as drastically and the corticosterone content remained unchanged.

Table 1 Plasma corticosteroids concentration (ng/ml) in normal controls and depersonalization patients

	Cortisol	Cortisone	Corticosterone
Control group (n = 36)			
After catheter insertion	30.5 ± 2.65	22.48 ± 3.24	9.61 ± 1.69
Depersonalization group (n = 8)			
After catheter insertion	13.98 ± 0.95***	16.77 ± 2.54	13.90 ± 2.66
30 min after catheter insertion	11.91 ± 1.36	14.45 ± 2.63	10.45 ± 2.01
15 min after placebo infusion	10.21 ± 1.09	13.84 ± 2.22	9.16 ± 1.10
15 min after naloxone infusion (0.4 mg)	11.53 ± 2.55	15.90 ± 2.56	7.97 ± 1.20
15 min after naloxone infusion (4 mg)	18.64 ± 3.35	20.33 ± 3.17	9.93 ± 2.01

***$p < 0.001$ between depersonalization and control groups.

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Discussion

Previous attempts to use naloxone for treating mental disorders proved to be unsuccessful (Abrams *et al.*, 1978; Volavka *et al.*, 1982; Keuler *et al.*, 1996) and an insignificant positive effect of short duration was recorded only in case of mania (Janowsky *et al.*, 1983). The opioid system seems to play an insignificant role in the pathogenesis of the endogeneous depression (Banki and Araio, 1987). As mentioned above, we used indirect data which suggested the importance of the opioid system in the pathogeneses of depersonalization, i.e. some depersonalization symptoms resemble the effect of morphine and depersonalization arises as a reaction to an acute emotional stress, which causes endorphin secretion.

The positive therapeutic effect of the opioid receptor blocker, naloxone, offers some evidence for the implication of the opioid system in the pathogenesis of depersonalization. This role is also confirmed by the influence of naloxone on the cortisol secretion in depersonalization patients: the low level of cortisol in depersonalization patients could be explained by the fact that endogeneous opioids inhibit CRF secretion. By blocking the action of endorphins, naloxone increases the cortisol secretion (Delitala *et al.*, 1994). The depersonalization patients were found to have a much lower cortisol content in plasma, which was drastically increased by naloxone. The increase of cortisol level coincided in time with the therapeutic effect of naloxone. There was a reduction of depersonalization symptoms without any signs of anxiety.

Our data do not provide sufficient evidence to conclude whether the therapeutic effect of naloxone is only related to the blockade of the opioid receptors or to some other factors that affect the opioid system. In most patients, the positive action of naloxone developed during the first hours after the infusion and, in many, the improvement lasted more than 24 h. Because the half-life of naloxone is approximately 60 min, this suggests that naloxone increased the patients' therapeutic sensitivity to the drugs that were previously not very effective for these particular patients.

One naloxone infusion was sufficient to entirely eliminate or considerably reduce all the symptoms of depersonalization in four patients who had a relatively recent depersonalization syndrome. However, some symptoms recorded prior to depersonalization reappeared and were easily treated by conventional medicine. Our previous data on the positive effect of large doses of benzodiazepines on depersonalization (Nuller, 1982) are evidence for the close relationship between depersonalization and anxiety. In most cases of chronic depersonalization, syndrome reduction was not accompanied by manifestation of affective symptoms. Here, depersonalization seems to be unrelated to anxiety and might become autonomous. The change of sensitivity in opioid receptors may be important in cases of chronic depersonalization.

In conclusion, some clinical manifestations of depersonalization, such as analgesia, the suppression of corticosteroid secretion and especially the positive therapeutic effect of the opioid receptor blocker, naloxone, offer evidence for the implication of the opioid system in the pathogenesis of depersonalization.

Address for correspondence

Professor Yuri L. Nuller
The Psychopharmacological Department
Bekhterev Psychoneurological Research Institute
3 Bekhterev St
St-Petersburg 193019
Russia
Email: nuller@J3971.spb.edu

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