Persistent Analgesia in Former Opiate Addicts Is Resistant to Blockade of Endogenous Opioids

Peter M. Liebmann, Michael Lehofer, Maximilian Moser, Rudolf Hoehn-Saric, Thomas Legl, Günter Pernhaupt, and Konrad Schauenstein

Key Words: Opiate dependence, pain, sensitivity, cold pressor test, endogenous opioid system, endogenous pain control, naltrexone

BIOL PSYCHIATRY 1997;42:962–964

Introduction

Besides a psychosocial disposition, pathophysiological factors may account for opiate dependence, as well as for the extremely high relapse rate in opiate addicts. These pathophysiological factors are of obvious clinical interest, as they may enable the future development of efficient and specific therapeutical interventions, and diagnostic tools to detect early the risk for relapse. We therefore are interested in characterizing pathophysiological factors possibly involved in substance dependence and relapse.

Some 30 years ago Dole and Nyswander (1967) postulated opiate dependence being a "metabolic disease" based on a deficiency of endogenous opioids. In view of the findings that the brain stem centers responsible for physical opiate dependence—the periaqueductal grey (Bozarth and Wise 1984) and the locus coeruleus (Maldonado and Koob 1993)—are also the centers of endogenous pain control (Watkins and Mayer 1982; Jensen 1986; Lipp 1991), we investigated pain sensitivity in detoxified opiate-dependent individuals who had abstained for at least 1 month in long-time rehabilitation (ex-addicts). It was found that ex-addicts showed a significantly decreased pain sensitivity in a cold pressor test as compared to controls (Liebmann et al 1994). Furthermore, we recently found evidence for a decreased nociceptive sensitivity to have existed already before dependence occurred in these individuals (Lehofer et al 1997). This decreased nociceptive sensitivity thus may be related to the development and maintenance of drug dependence.

A decreased nociception in relation to the development of heroin dependence might contradict the notion of a deficient endogenous opioid system in opiate addicts, however, since endogenous opioids are important pain-relieving substances (Lipp 1991). The aim of this study was therefore to clarify whether an increased endogenous opioid tone could account for the decreased pain sensitivity in ex-addicts, as it is the case in pain-insensitive healthy subjects (Buchsbaum et al 1977), or in cold pressor test induced analgesia (Jungkunz et al 1983), where in both cases the specific opioid antagonist naloxone could lower the pain thresholds.

Methods and Materials

A group of 31 clinically detoxified, unmedicated opiate addicts (for descriptors see Table 1), who participated in a long-term rehabilitation program at the rehabilitation center "Grüner Kreis" (Aspang, Austria), was investigated. Continued abstinence was verified by urine drug screens. Dependence was defined according to DSM-III-R. Beginning of detoxification was defined as the time after termination of drug intake. Absence of withdrawal symptoms, except minor autonomic symptoms, like restlessness or minor sleep disturbances, marked the end of detoxification and beginning of the 2 years of rehabilitation in a therapeutic community. Thirty-one healthy volunteers, who had never been opioid dependent, served as controls for normal pain

From the Institute of General and Experimental Pathology, University of Graz, Graz, Austria (PML, KS); Institute of Psychiatry, University of Graz, Graz, Austria (ML); Institute of Physiology, University of Graz, Graz, Austria (MM); Johns Hopkins School of Medicine, Department of Psychiatry, Baltimore, Maryland (RHS); and Drug Rehabilitation Center "Grüner Kreis," Aspang, Austria (TL, GP).

Address reprint request to Peter M. Liebmann, PhD, Institute of General & Experimental Pathology, University of Graz, Mozartgasse 14/II, A-8010 Graz, Austria.

Received March 26, 1996; revised September 6, 1996.

0006-3223/97/$17.00
PII S0006-3223(97)00337-5

Table 1. Characteristics of the Control vs. the Ex-Addict Group (Mean ± SD)

	Controls	Ex-addicts
Age (years)	31.7 ± 9.5	27.1 ± 6.3
% male	40	68
n	31	31
Duration of drug dependence (years)		6.5 ± 4.2
Duration of rehabilitation (months)		8.1 ± 4.7

sensitivity (for descriptors see Table 1). Written informed consent was obtained from all participants.

We measured pain sensitivity after oral administration of the specific μ-antagonist naltrexone (Nemexin®, 50 mg, kindly provided by Willvonseder & Marchesani, Vienna) in a placebo-controlled single-blind crossover study with a 3-week washout period between the two experimental sessions. Naltrexone has a long biological half-life (Martin et al 1973), and it was demonstrated to completely block the psychotropic effects of heroin in former heroin addicts 24 hours after a single dose of 50 mg (Resnick et al 1974). Therefore, the response to the medication was examined 24 hours after treatment.

Pain sensitivity was determined with a cold pressor test, which is established to be the best among presently used laboratory methods to simulate quality, duration, and urgency of clinical pain (Turk et al 1983). The cold pressor test was done as recently described (Liebmann et al 1994), recording the times until i) first pain sensation occurred (pain threshold), and ii) pain was no longer tolerable (tolerance threshold) during a cold pressor stimulus. Smoking was prohibited for at least 1 hour prior to the pain measurement. After the test the corresponding subjective maximal pain intensities during the tests were recorded using a nine-point visual digital scale, from 1 (no pain) to 9 (extreme pain).

Pain and tolerance threshold levels were normalized by logarithmization. To test associations of the dependent variables pain threshold, tolerance threshold, and pain intensity with age, length of rehabilitation, and the categorical variables sex, treatment (with and without naltrexone), and proband group (control or ex-addict), a stepwise regression was performed with the SYSTAT 5.01 software package.

Results

The statistical analysis revealed a significant ($p < 0.02$) difference in pain threshold between controls and ex-addicts (Table 2), but no association with age, sex, length of rehabilitation, or experimental treatment. No association of tolerance threshold or pain intensity was found with any of the independent variables tested.

Discussion

In accordance with earlier results (Liebmann et al 1994; Lehofer et al in press), ex-addicts showed a decreased pain sensitivity in a cold pressor test indicated by the increased pain threshold at similar pain intensity. In healthy subjects reduced pain sensitivity has been attributed to an increased endogenous opioid tone, since the blockade by naloxone increased pain sensitivity in less pain-sensitive healthy volunteers (Buchsbaum et al 1977). In contrast to this, naltrexone in ex-addicts in the present experiment had no effect on the decreased pain sensitivity, indicating that an increased opioid tone is not responsible for the higher pain threshold in these patients. We therefore conclude that nonopioid mechanisms of the endogenous pain control system are up-regulated in ex-addicts.

Why should they be up-regulated? From animal experiments it is known that the response to stressors producing nonopioid stress-induced analgesia is higher when the opioid pathways are blocked (Kirchgessner et al 1982; Yoburn et al 1987; Grisel et al 1993), indicating that opioid and non-opioid pain suppression systems are reciprocally inhibitory. Transferring these results into humans, a primary dysfunction of central opioid pathways in ex-addicts may be compensated by enhanced opioid-independent mechanisms. From these considerations a primary dysfunction of endogenous opioid pathways in ex-addicts seems likely.

But why are they less pain sensitive than healthy controls? Could their reduced pain sensitivity be some sort of stress analgesia? Very recently we could show that "nervousness" is accompanied with reduced pain sensitivity (Lehofer et al 1997), and that ex-addicts indeed rated themselves as afflicted with significantly increased nervousness (Liebmann et al in press); however, a psychic stress-induced analgesia in healthy volunteers can be blocked by the opioid antagonist naloxone (Bandura et al 1988), indicating that a normal psychic stress-induced analgesia involves at least in part opioid-dependent mechanisms. In contrast to that, the pain sensitivity in ex-addicts does not respond to opioid blockade, which argues against a normal stress-induced analgesia in these patients.

Taken together our data indicate a shift toward nonopioid analgesia in ex- addicts, most likely in response to a loss of functional central opioid pathways. This lasting compensatory up-regulation of opioid-independent pathways might explain

Table 2. Pain Measures in Placebo- and Naltrexone-Treated Ex-Addicts vs. Healthy Controls, Showing a Lack of Naltrexone Effects in Ex-Addicts in Spite of an Increased Pain Threshold (Mean ± SD)

	Log pain threshold	*n*	Log tolerance threshold	*n*[a]	Pain intensity	*n*
Controls	1.404 ± 0.297	31	1.82 ± 0.323	15	5.469 ± 2.615	31
Ex-addicts placebo	1.564 ± 0.209[b]	31	1.963 ± 0.312	16	6.27 ± 2.08	30
Ex-addicts naltrexone	1.587 ± 0.245[b]	29	1.97 ± 0.267	16	5.683 ± 1.967	30

[a] *n* drops since in about 50% of the probands the tolerance threshold was not reached (they could stand the pain over the full measuring period of 7 min).
[b] $p < .02$ vs. healthy controls.

why endogenous opioid pathways never return to normal, and therefore why craving and the risk for relapse persist for years. Our results therefore argue in favor of an intrinsic dysfunction of central opioid pathways in opiate dependence.

References

Bandura A, Cioffi D, Taylor CB, Brouillard ME (1988): Perceived self-efficacy in coping with cognitive stressors and opioid activation. *J Pers Soc Psychol* 55:479–488.

Bozarth M, Wise RA (1984): Anatomically distinct opiate receptor fields mediate reward and physical dependence. *Science* 224:516–517.

Buchsbaum MS, Davis GC, Bunney WE Jr (1977): Naloxone alters pain perception and somatosensory evoked potentials in normal subjects. *Nature* 270:620-622.

Dole VP, Nyswander M (1967): Heroin addiction—A metabolic disease. *Arch Intern Med* 120:19–24.

Grisel JE, Fleshner M, Watkins LR, Maier SF (1993): Opioid and nonopioid interactions in two forms of stress-induced analgesia. *Pharmacol Biochem Behav* 45:161–172.

Jensen TS (1986): Endogenous antinociceptive systems: Studies on spinal and supraspinal modulating mechanisms with particular reference to monoaminergic and opioid systems. *Acta Neurol Scand Suppl* 108:1–35.

Jungkunz G, Engel RR, King UG, Kuss HJ (1983): Endogenous opiates increase pain tolerance after stress in humans. *Psychiatry Res* 8:13–18.

Kirchgessner AL, Bodnar J, Pasternak GW (1982): Naloxazone and pain-inhibitory systems: Evidence for a collateral inhibition model. *Pharmacol Biochem Behav* 17:1175–1179.

Lehofer M, Liebmann PM, Moser M, Legl T, Pernhaupt G, Schauenstein K, et al (1997): Decreased nociceptive sensitivity: A biological risk marker for opiate dependence? *Addiction* 92:163–166.

Lehofer M, Liebmann PM, Moser M, Schauenstein K, Zapotoczky HG (in press): Nervousness and pain sensitivity: I. A positive correlation. *Psychiatry Res.*

Liebmann PM, Lehofer M, Schönauer-Cejpek M, Legl T, Pernhaupt G, Moser M, et al (1994): Pain sensitivity in former opioid addicts. *Lancet* 344:1031–1032.

Liebmann PM, Lehofer M, Moser M, Hoehn-Saric R, Legl T, Pernhaupt G, et al (in press): Nervousness and pain sensitivity: II. Changed relation in ex-addicts as a predictor for early relapse. *Psychiatry Res.*

Lipp J (1991): Possible mechanisms of morphine analgesia. *Clin Neuropharmacol* 14:131–147.

Maldonado R, Koob GF (1993): Destruction of the locus coeruleus decreases physical signs of opiate withdrawal. *Brain Res* 605:128–138.

Martin WR, Jasinski DR, Mansky PA, Lexington K (1973): Naltrexone, an antagonist for the treatment of heroin dependence. *Arch Gen Psychiatry* 28:784–791.

Resnick RB, Volavka J, Freedman AM (1974): Studies on EN-1639 (naltrexone) a new narcotic antagonist. *Am J Psychiatry* 131:646–650.

Turk DC, Meichenbaum D, Genest M (1983): *Pain and Behavioral Medicine: A Cognitive-Behavioral Perspective.* New York: Guilford, p. 452.

Watkins LR, Mayer DL (1982): Organization of endogenous opiate and nonopiate pain control systems. *Science* 216:1185–1192.

Yoburn BC, Truesdell LS, Kest B, Inturrisi CE, Bodnar RJ (1987): Chronic opioid antagonist treatment facilitates nonopioid, stress-induced analgesia. *Pharmacol Biochem Behav* 27:525–527.