PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 162, 392–395 (1979)

Pain Perception in Drug-Free and in Methadone-Maintained Human Ex-Addicts (40689)

ANN HO AND VINCENT P. DOLE

The Rockefeller University, New York, New York 10021

It has been asserted that narcotic addicts are more sensitive to pain (1) and less able to tolerate discomfort (2) than nonaddicts. On the other hand, concern has been expressed that the perception of pain by methadone-maintained ex-addicts might be impaired by a supposed analgesic effect of their daily narcotic medication (3). The study reported here investigated the pain threshold and pain tolerance of ex-addicts with long histories of heroin addiction, and of age-matched, never-addicted siblings of addicts. Resting blood pressure was determined before and after testing to further explore the changed autonomic responsivity found in the early postaddict state (4, 5).

Materials and methods. Subjects and drugs. Thirty men and women served as *S*s in three agematched groups of 10 each: drug-free ex-addicts (DFE), methadone-maintained ex-addicts (MME), and nonaddict siblings (NAS). Paid volunteers were recruited from a group of potential *S*s who had already completed a Cornell Medical Index and a 1-hr drug and life-history interview. This larger subject pool included ex-addicts contacted through abstinence drug treatment programs and methadone maintenance clinics in New York City and their nonaddict siblings whenever possible. *S*s were selected so that there were no significant differences between groups in age, ethnic origin, sex, or work status. Altogether there were 24 men and six women; 16 *S*s were black, 6 were Spanish, and 8 were white. Relevant aspects of the drug history of MME and DFE are shown in Table I. The two ex-addict groups were comparable in addiction history and in length of either methadone maintenance or abstinence treatment. One-way analyses of variance were used to examine group differences in the subject characteristics summarized in Table II. *S*s in both MME and DFE reported more medical problems and had completed fewer years of school than did those in NAS. Analyses of urine specimens collected just before the individual testing sessions were negative for amphetamines, barbiturates, and narcotics in DFE and NAS and were positive for methadone only in MME (6). The mean daily methadone dose in MME was 80 mg, with a range of 60–100 mg, and with a mean of 18 months since any dose change.

Procedure. The procedure was described in detail to the *S* before the testing began and a written consent was obtained with the understanding that the *S* could withdraw from the experiment at any time. All *S*s completed the experiment. All tests were conducted in the afternoon in an air-conditioned room. The *E* avoided systematic knowledge of the status of each *S*, although occasionally there were visible scars on the arm or a spontaneous remark of the *S* revealed group status.

Immersion of the hand in an ice-water bath was the stimulus used to produce what has been described as "deep aching pain" (7), the intensity of which has been shown to increase with the time the hand is immersed (8). The *S* was asked to report when "the feeling of cold turns into a feeling of pain" (threshold latency measured by *E* in seconds) and to remove the hand from the ice water when "it becomes too uncomfortable to continue" (tolerance measured in seconds). The trial was ended by *E* after 60 sec if *S* had not already said "stop" and withdrawn the hand since cold-produced pain intensity reaches its maximum at about 1 min and subsides thereafter (9). (The eight *S*s for whom this was necessary were distributed among the three groups: MME, 2; DFE, 2: NAS, 4). During the tests, the *S* sat on a swivel chair between two water baths that could be reached comfortably with either hand. Each trial began with a 2-min immersion of the left hand in a 30° adapting bath. The *S* quickly dried that hand and plunged it to the wrist in ice water (1°). This procedure was alternated between hands for a total of six trials, three with each hand, over a period of about 20 min.

Blood pressure was recorded with the *S* in

0037-9727/79/110392-04$01.00/0

TABLE I. DRUG HISTORY OF MME AND DFE[a]

	MME	DFE
Total years addicted	9.5 ± 2.1	9.0 ± 1.9
Years actively addicted	6.9 ± 1.1	5.2 ± 1.0
Years methadone maintained	3.1 ± 0.6	—
Years drug free	—	3.7 ± 0.7

[a] Years actively addicted represents time addicted to heroin "on the street" excluding time spent in institutions or "clean on the street." Values are expressed as means ± SE.

a supine position at 5-min intervals three times before and three times after the series of pain tests.

Data treatment. The first pain test with each hand was considered a practice trial and was discarded. Since the distributions of both pain threshold and pain tolerance were skewed, log transformations of the data were made before three-way (groups × hand × trial) analyses of variance with repeated measures were performed (10). Resting systolic and diastolic blood pressure measurements were also separately subjected to three-way (group × before-after × order-of-measurement) analyses of variance.

Results. The pain threshold of the left hand was slightly but significantly lower than that of the right hand (see Table III) as had been reported for a different subject population (11, 12). Tolerance was also slightly lower in the left hand but this effect was not significant at the 0.05 level. There were no other significant main effects or interactions between groups, hands, or trials.

Three separate statistical comparisons were made to test the specific hypotheses of pain perception in narcotics addicts mentioned above. To examine the directional hypothesis suggested by Knowles *et al.* (1) that exaddicts are more sensitive to pain than nonaddicts, the pooled scores of DFE and MME were compared to those of NAS. This comparison yielded an $F(1, 27) = 3.61$, $P < 0.05$ (one tailed), indicating that the ex-addicts had a significantly lower pain threshold than the nonaddicts. A similar comparison failed to support the claim of Martin and Inglis (2) that pain tolerance is lower in ex-addicts. Furthermore, an orthogonal comparison of the two ex-addict groups showed no significant difference in either threshold or tolerance. These data do not support the contention of Lennard *et al.* (3) that stable daily doses of methadone "reduce perception" or "dampen feeling."

Nonaddict subjects had significantly lower resting diastolic blood pressures than the two ex-addict groups (see Table IV). Systolic pressures were also lower but the F obtained fell just outside the 0.05 region of rejection. There is a significant group × before–after interaction indicating that after the testing session, diastolic pressures were higher in the nonaddicts but not in the ex-addicts. There were no significant elevations of systolic pressure in any group following the ice-water stimulus.

Discussion. The absence of a significant difference in either the threshold or tolerance to cold-induced pain between the two ex-addict groups is of interest as it relates to the endorphin–opiate receptor systems. In subjects with a 60–100 mg/day intake of methadone, and an average concentration in plasma of about 3×10^{-7} M (13), an appreciable fraction of the endogenous ligand must be chronically displaced from the opiate receptors. The pain perception test used in this study should have been sensitive enough to reveal even a small difference between the two groups, if one existed, since it did show a significant difference between the hands of the same subject, and between the combined scores of the ex-addict groups and the nonaddict sibling controls. The similarity in response to cold-induced pain in two groups with different ligands associated with their opiate receptors suggests either that this receptor system does not affect the response to experimentally induced pain (14) or that methadone in the stabilized patient serves as a functional equivalent of the natural ligand. Indeed, two studies on human pain percep-

TABLE II. AGE, EDUCATION, AND SYMPTOM REPORTS[a]

	MME	DFE	NAS
Years of age	30.7	31.2	31.1
	±2.2	±1.9	±1.5
Years of education*	10.9	11.4	13.1
	±0.4	±0.2	±0.5
Positive responses to Cornell Medical Index**	21.9	26.9	8.5
	±4.2	±4.9	±1.8

[a] Values are expressed as mean ± SE.

* $F(2,25) = 8.12$, $P < 0.001$; total $n = 28$ due to missing data.

** $F(2,27) = 4.51$, $P < 0.05$.

TABLE III. PAIN THRESHOLD AND PAIN TOLERANCE[a]

	Threshold		Tolerance	
	Left hand*	Right hand	Left hand**	Right hand
MME	1.1852 ± 0.0691 (15.3 sec)	1.2197 ± 0.0808 (16.6 sec)	1.4090 ± 0.0592 (25.6 sec)	1.4539 ± 0.0641 (28.4 sec)
DFE	1.1001 ± 0.0531 (12.6 sec)	1.1878 ± 0.0501 (15.4 sec)	1.4133 ± 0.0589 (25.9 sec)	1.4743 ± 0.0437 (29.8 sec)
NAS	1.2838 ± 0.0440 (19.2 sec)	1.3318 ± 0.0579 (21.5 sec)	1.5104 ± 0.0546 (32.4 sec)	1.5029 ± 0.0552 (31.8 sec)

[a] Values are expressed as the mean ± SE of the log transform of two determinations with each hand. Values in parentheses are geometric means (antilogs of the means of transformed data) expressing the central tendency in seconds.

* Left-hand < right-hand threshold $F(1,27) = 9.11$, $P < 0.01$.

** Left-hand < right-hand tolerance $F(1,27) = 4.09$, $P < 0.10$.

TABLE IV. RESTING SYSTOLIC AND DIASTOLIC BLOOD PRESSURE[a]

	Systolic* (mm Hg)		Diastolic** (mm Hg)	
	Before	After	Before	After
MME	112 ± 4	112 ± 4	80 ± 4	78 ± 2
DFE	122 ± 6	122 ± 6	81 ± 4	82 ± 4
NAS	106 ± 4	107 ± 4	64 ± 2	71 ± 4***

[a] Values are expressed as means ± SE of the three measures made before and the three made after the pain-testing session.

* Group $F(2,27) = 3.22$, $P < 0.10$.

** Group $F(2,27) = 5.18$, $P < 0.05$.

*** Group × before–after interaction $F(2,27) = 3.48$, $P < 0.05$.

tion following naloxone have failed to demonstrate the involvement of endorphins in experimental pain of nonaddicts (15, 16). In practical terms, the important finding is that the perception of somatic pain is not impaired in the methadone patients, despite the daily ingestion of a medication that would be a powerful analgesic for nontolerant subjects.

Prystav (4) found short-term drug-free addicts to show no rise in diastolic blood pressure following various experimental presentations including cold pressor stimulation, while the pressure of control *S*s rose. The results reported here indicate a similar lack of blood pressure response in long-term ex-addicts, both drug free and methadone maintained, when compared to a matched nonaddict group. The differing experimental procedures of the Prystav study (including presentations of white noise, strobe light, cold pressor stimulation of the left foot for several standard 1-min exposures, lack of pain perception tasks) make the parallel finding the more interesting.

The findings of this study indicate a differing physiological response to cold-produced pain in ex-addicts both methadone maintained and drug free compared to closely matched nonaddicts. Since the preaddiction pain sensitivity and blood pressure response of the ex-addicts are not known, there is no way to determine the origin of these differences, whether they predated or were the result of narcotic addiction. These different responses to a pain stimulus were found after prolonged abstinence in the case of one ex-addict group (DFE *S*s were drug free more than 3 years) and suggest a chronic physiological difference. Finally, of perhaps greatest clinical importance is the finding that in stablized methadone-maintained ex-addicts (MME *S*s' methadone dosage had not recently been raised or lowered) responses to pain do not differ from matched drug-free ex-addicts.

Summary. Cold-induced pain threshold and pain tolerance were measured in drug-free ex-addicts (DFE), in methadone-maintained ex-addicts (MME), and in age-matched nonaddict siblings (NAS). Multiple responses to an ice-water stimulus were obtained for each hand. Resting systolic and diastolic blood pressures were determined across a 15-min period both before and immediately after the pain-testing session. Pain threshold of both ex-addict groups (DFE and MME) was lower than that of NAS. Pain tolerance was slightly but not significantly lower. Ex-addicts further differed from nonaddicts in an autonomic response to the experimental situation: The diastolic blood pressure of nonaddicts rose following cold pressor stimulation but there was no rise in

the ex-addict groups. Methadone-maintained ex-addicts do not differ from drug-free ex-addicts in pain threshold, pain tolerance, or blood pressure response.

We thank the directors, particularly Dr. Mitchell S. Rosenthal of Phoenix House, the staff, and patients of various drug-free programs and methadone clinics for their cooperation in contacting or serving as subjects. The study was supported by NIDA Grant DA-00390-01 and by New York State Office of Drug Abuse Services Grant C-107653.

1. Knowles, R., Lahari, S., and Anderson, G., *in* "Methadone Maintenance" (S. Einstein, ed.). Marcel Dekker, New York (1971).
2. Martin, J. E., and Inglis, J., Brit. J. Social Clin. Psychol. **4,** 224 (1965).
3. Lennard, H. L., Epstein, L. J., and Rosenthal, M. S., Science **176,** 881 (1972).
4. Prystav, G. H., Psychophysiology **12,** 170 (1975).
5. Prystav, G. H., J. Gen. Psychol. **94,** 259 (1976).
6. Dole, V. P., Crowther, A., Johnson, J., Monsalvatge, M., Biller, B., and Nelson, S. S., N. Y. State J. Med. **72,** 471 (1972).
7. Hines, E. A., and Brown, G. E., Staff Meetings of the Mayo Clinic **7,** 332 (1932).
8. Hilgard, E. R., Amer. Psychol. **24,** 103 (1969).
9. Wolf, S., and Hardy, J. D., J. Clin. Invest. **20,** 521 (1941).
10. Winer, B. J., "Statistical Principles in Experimental Design." McGraw–Hill, New York (1971).
11. Murray, F. S., and Safferstone, J. F., J. Comp. Physiol. Psychol. **71,** 83 (1970).
12. Murray, F. S., and Hagen, B. C., J. Comp. Physiol. Psychol. **84,** 639 (1973).
13. Dole, V. P., and Kreek, M. J., Proc. Nat. Acad. Sci. USA **70,** 10 (1973).
14. Goldstein, A., Science **193,** 1081 (1976).
15. El-Sokby, A., Dostrovsky, J. O., and Wall, P. O., Nature (*London*) **263,** 783 (1976).
16. Grevert, P., and Goldstein, A., Proc. Nat. Acad. Sci. USA **74,** 1271 (1977).

Received October 4, 1977. P.S.E.B.M. 1979, Vol. 162.