POSSIBLE ANTIDEPRESSIVE EFFECTS OF OPIOIDS: ACTION OF BUPRENORPHINE

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INTRODUCTION

The euphorogenic and anxiolytic properties of opiates [1] and of endorphins [2] prompt questions as to the possibility that a defectively operating endorphinergic system may represent a causative factor in the pathogenesis of endogenous depression. Though from biochemical and pharmacological data the evidence in support of this hypothesis is weak (cf. ref. 3) it, nevertheless, requires additional evaluation. However, irrespective of the presence of a hypothetical constitutional deficit of endogenous morphinomimetic substances compensated for by an exogenous supply in the therapy of depressed patients, the question arises if, independently from such a possible type of metabolic dysfunction in depression, there may exist direct pharmacodynamic therapeutic effects of opioids in depressive syndromes. Since anxiety and sleep disturbances, in addition to melancholia, make up an integral part of the psychopathology of depression, from their profile of action, it may be anticipated that opioids could be highly effective, therapeutically, in depressive illness.

Indeed, since the time of Emil Kraepelin [4] the "opium cure" has been recommended for the treatment of depressed patients, employing slowly increasing and later decreasing dosages of tinctura opii [5] and of other opiates.[6] Interestingly, according to reports of that time, although a standardized evaluation of the therapeutic efficacy was, and is, lacking, this treatment was effective and did not result in opiate addiction, possibly, since the doses applied were comparatively low. Later, Fink *et al.*[7] applied the mixed agonist/antagonist cyclazocine (1.0–3.0 mg) in 10 severely depressed patients and observed a strong antidepressive effect, in particular concerning the items "depressed mood" and "apathy." A further clinical evaluation of possible beneficial effects of opiates has been deferred, possibly owing to the psychotomimetic effects of cyclazocine and, furthermore, in view of the fact that the discovery of tricyclic antidepressants and of MAO-inhibitors opened a new era in the pharmacotherapy of depressive syndromes. Interestingly, immediately after the discovery of the endorphins, which shed new light onto the possible psychotropic effects of an activation of opiate receptors, new attempts were initiated in the evaluation of the possible antidepressive effects of opioids. Kline *et al.*[2] were the first to perform clinical trials in different types of psychiatric disorders (schizophrenia, depression, neuroses) by use of β-endorphin infusions (1.5–6.0 mg) and observed in two depressed patients, in an open design, positive effects of this treatment. Angst *et al.*,[8] also in an open trial, investigated the possible antidepressive action of infusions of 10 mg of β-endorphin and detected a switch to hypomania/mania in three of six depressed patients. Subsequently, double-blind trials as to the possible antidepressant efficacy of β-endorphin have been

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performed by two groups.[9, 10] Gerner *et al.*[9] reported a significant improvement 2 to 4 hours after β-endorphin infusions, as compared to placebo treatment in 10 depressed patients, whereas Pickar *et al.*[10] found no significant change in 4 depressed patients after β-endorphin therapy. The application of the synthetic enkephalin analogue FK 33-824 in 10 depressed patients produced a sizable improvement in 3 of the patients and a tranquilizing effect in 4 of them.[11]

Interestingly, the investigation as to the possible value of opioids in antidepressive therapy were not confined to endogenous morphinomimetic substances or their derivatives but were—in line with the attempts performed prior to the studies of Fink *et al.*[7]—also undertaken with opiates, such as morphine and other opium alkaloids in clinical therapeutic trials. Gold *et al.*,[12] for example, presented data suggestive of a potential antidepressant and anxiolytic/antipanic effects of opiates. On the other hand, Extein *et al.*[13] reported only a slight antidepressive effect of 5.0 mg morphine in 10 patients with major depressive disorders (open study), whereas in a double-blind investigation in 6 depressed in-patients, 5.0 mg methadone proved not different in effect from placebo.

Another basis from which to speculate as to possible antidepressive properties of opioids lies in the fact that electroconvulsion, which is certainly one of the most efficacious and rapidly acting somatic treatments in depression, possesses endorphin-activating properties. As shown by Belenky and Holaday [14] in animal experiments, electroconvulsion induces a spectrum of vegetative, naloxone-reversible changes, which apparently reflect an EC-effected activation of particular endorphinergic systems. Similar conclusions may be derived from the estimation of plasma β-endorphin immunoreactivity in depressed patients before and after electroconvulsion, which exhibits a highly significant increase after this procedure.[15] Interestingly, these endorphin-mobilizing properties are not confined to electroconvulsion but also are exhibited by other physical methods used in the past in the treatment of psychotic disorders (e.g. cold-water stress,[16] insulin coma,[17] rotational stress [cf. ref. 18]). Additionally, the stressful procedure of hemodialysis, which in some cases apparently exerts antidepressant effects,[19] unequivocally induces an elevation of plasma β-endorphin immunoreactivity,[20] an effect which is possibly also exhibited by sham-dialysis. Therefore, some of the controversial results concerning the action of hemodialysis in different types of psychoses may be explained in terms of an nonspecific stress effect of this procedure.

Investigations as to a possible antidepressant effect of the opiate mixed agonist/antagonist buprenorphine [21] are suggested not only by the total body of evidence concerning the possible antidepressive effect of opioids, reviewed above, but also by the observations that it, as shown by Mello and Mendelson,[22] has highly positive subjective effects in opiate addicts. Furthermore, the finding that buprenorphine has mood-improving effects in postoperative patients [23] and the very important fact that this strong analgesic substance is devoid of psychotomimetic effects and has a very low abuse potential [24, 25] suggests the performance of clinical trials with the aim of developing a new opioid substance with a strong antidepressant potency and a high degree of drug safety.

Methods

The study was performed by use of a double-blind $A_1/B/A_2$-design ($A_{1/2}$ = placebo; B = buprenorphine). Ten patients who met the research

diagnostic criteria [26] for major depressive disorder gave their informed consent to participate in the study. The duration of the three therapeutic phases varied between: A_1: 1–7 days, B: 5–8 days; A_2: 0–4 days. The patients were free of conventional thymoleptic drugs. Before the beginning of the trial, a wash-out period of 4 days was performed. During the buprenorphine treatment phase, two sublingual tablets (0.2 mg per day) were given at 8:30 and 16:30 h. Psychopathological evaluation was performed by a trained psychiatrist every two days in the afternoon by use of the IMPS [27] and the Hamilton scale for depression.[28] Additionally, the global impression of depression and, as a screening of side effects, the symptoms "nausea," "vomiting," "dizziness," and "euphoria" were evaluated by use of the VBS (*V*erlaufs-*B*eurteilungs-*S*kala).[29]

RESULTS

The mean results of the Hamilton-scores before (A_1), during (B_1; B_2; B_3) and after (A_2) buprenorphine treatment are depicted in FIGURE 1. The data

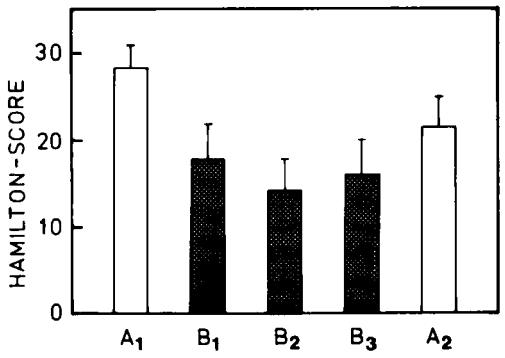

FIGURE 1. Averaged Hamilton-scores of 10 depressed patients before (A_1), during (B_1-B_3), and after (A_2) buprenorphine treatment. Bars: SEM; for details see text.

B_1–B_3 represent the average values of the Hamilton-score at the beginning of the blind buprenorphine treatment (B_1), in the middle of buprenorphine treatment phase (B_2), and at the end of buprenorphine treatment (B_3). A_2 represents the average data of the Hamilton-scores at the end of the second placebo treatment period. As can be seen in FIGURE 1, there is a strong reduction in the Hamilton-scores during the phases B_1–B_3 in comparison with the placebo phases A_1, and, to a lesser degree, also in comparison with the second placebo phase A_2. These differences are highly significant ($p \leq 0.02$, Wilcoxon-test).

An evaluation of the single data of individual patients (data not shown) reveals that about 50% of the patients responded very strongly to buprenorphine, whereas the other 50% were, apparently, nonresponders. Since practically all of the patients included in the study were nonresponders to conventional thymoleptic therapy, this is a significant result. Most of the patients experienced some degree of slight nausea, dizziness and sedation (vomiting in one case) in the course of the study, but these side effects, with the exception of the one case of vomiting, never became a problem during therapy.

Discussion

As shown in the present investigation, the mixed opiate agonist/antagonist buprenorphine exhibits antidepressant properties in cases not responding to conventional thymoleptic therapy. This is a remarkable finding, since for this type of patient, an inevitable consequence would be the application of electroconvulsion, a somatic type of therapy which, in view of some of its side effects [30] and therapeutic risks [31] is not a desirable choice in the treatment of psychiatric patients. Therefore, the intriguing possibility has to be considered that the type of therapy indicated here may represent a way of mimicking by chemical means the neurobiologically therapeutic effects of electroconvulsion; one can thus speculate that other physical and/or chemical means of inducing endorphin activation (e.g. inhibition of enkephalinases) may, also, in the future, play a therapeutic role in the treatment of endogenous depression.

References

1. Martin, W. R., Ed. 1977. Drug Addiction. I. Morphine, Sedative-Hypnotic and Alcohol Dependence. Handbuch der Experimentellen Pharmakologie, Vol. 45. Springer. Berlin-Heidelberg-New York.
2. Kline, N. S., C. H. Li, H. E. Lehmann, A. Lajtha, E. Laski & T. Cooper. 1977. β-Endorphin-induced changes in schizophrenic and depressed patients. Arch. Gen. Psychiatry **34:** 1111–1113.
3. Emrich, H. M. 1981. A possible role of opioid substances in depression. *In* Typical and Atypical Antidepressants, Vol. 1: Clinical Practice. E. Costa & G. Racagni, Eds.: 77–84. Raven Press. New York.
4. Kraepelin, E. 1901. Einführung in die Psychiatrische Klinik. Joh. Ambrosius Barth-Verlag. Leipzig.
5. Kraepelin, E. 1927. Psychiatrie I. Joh. Ambrosius Barth-Verlag. Leipzig.
6. Weygandt, W. 1935. Lehrbuch der Nerven- und Geisteskrankheiten. Marhold-Verlagsbuchhandlung. Halle.
7. Fink, M., J. Simeon, T. M. Itil & A. H. Freedman. 1970. Clinical antidepressant activity of cyclazocine—a narcotic antagonist. Clin. Pharmacol. Ther. **11:** 41–48.
8. Angst, J., V. Autenrieth, F. Brem, M. Koukkou, H. Meyer, H. H. Stassen & U. Storck. 1979. Preliminary results of treatment with β-endorphin in depression. *In* Endorphins in Mental Health Research. E. Usdin, W. E. Bunney, Jr. & N. S. Kline, Eds.: 518–528. Macmillan. London.
9. Gerner, R. H., D. H. Catlin, D. A. Gorelick, K. K. Hui & C. H. Li. 1980. β-Endorphin. Intravenous infusion causes behavioral change in psychiatric inpatients. Arch. Gen. Psychiatry **37:** 642–647.
10. Pickar, D., G. C. Davis, S. C. Schulz, I. Extein, R. Wagner, D. Naber, P. W. Gold, D. P. van Kammen, F. K. Goodwin, R. J. Wyatt, C. H. Li & W. E. Bunney, Jr. 1981. Behavioral and biological effects of acute β-endorphin injection in schizophrenic and depressed patients. Am. J. Psychiatry **138:** 160–166.
11. Rüther, E., G. Jungkunz & N. Nedopil. 1981. Clinical effects of the synthetic analogue of methionine enkephalin FK 33–824. IIIrd World Congress of Biological Psychiatry, Stockholm. (Abstract)
12. Gold, M. S., A. L. C. Pottash, D. R. Sweeney, H. D. Kleber & D. E. Redmond. 1979. Rapid opiate detoxification: Clinical evidence of antidepressant and antipanic effects of opiates. Am. J. Psychiatry **136:** 982–983.
13. Extein, I., D. Pickar, M. S. Gold, P. W. Gold, A. L. C. Pottash, D. R. Sweeney, R. J. Ross, R. Rebard, D. Martin & F. K. Goodwin. 1981. Methadone and morphine in depression. Pharmacol. Bull. **17:** 29–33.

14. BELENKY, G. L. & J. W. HOLADAY. 1979. The opiate antagonist naloxone modifies the effects of electroconvulsive shock (ECS) on respiration, blood pressure and heart rate. Brain Res. **177:** 414–417.
15. EMRICH, H. M., V. HÖLLT, W. KISSLING, M. FISCHLER, H. LASPE, H. HEINEMANN, D. v. ZERSSEN & A. HERZ. 1979. β-Endorphin-like immunoreactivity in cerebrospinal fluid and plasma of patients with schizophrenia and other neuropsychiatric disorders. Pharmakopsychiatr/Neuro-Psychopharmakol. **12:** 269–276.
16. BODNAR, R. J., D. K. KELLY, M. BRUTUS & M. GLUSMAN. 1980. Stress-induced analgesia: Neural and hormonal determinants. Neurosci. Biobehav. Rev. **4:** 87–100.
17. HÖLLT, V., R. PRZEWLOCKI & A. HERZ. 1978. Radioimmunoassay of β-endorphin. Basal and stimulated levels in extracted rat plasma. Arch. Pharmacol. **303:** 171–174.
18. MILLAN, M. J. 1981. Stress and endogenous opioid peptides: A review. *In* The Role of Endorphins in Neuropsychiatry. H. M. Emrich, Ed. Modern Problems in Pharmacopsychiatry. **17:** 49–67. Karger. Basel.
19. SCHEIBER, S. C., I. COHEN, H. YAMAMURA, R. NOVAL & L. BEUTLER. 1981. Dialysis for schizophrenia: An uncontrolled study of 11 patients. Am. J. Psychiatry **138:** 662–665.
20. HÖLLT, V., G. HILLEBRAND, B. SCHMIDT & H. J. GURLAND. 1979. Endorphins in schizophrenia: Hemodialysis/hemoperfusion are ineffective in clearing β-leu^5-endorphin and β-endorphin from human plasma. Pharmakopsychiatr/Neuro-Psychopharmakol. **12:** 399–406.
21. LEWIS, J. W. 1980. Buprenorphine—a new strong analgesic. *In* Problems in Pain. C. Peck & M. Wallace, Eds.: 87–89. Pergamon Press. Oxford.
22. MELLO, N. K. & J. H. MENDELSON. 1980. Buprenorphine suppresses heroin use by heroin addicts. Science **207:** 657–659.
23. HARCUS, A. H., A. E. WARD & D. W. SMITH. 1980. Buprenorphine in post-operative pain: Results in 7500 patients. Anaesthesia **35:** 382–386.
24. JASINSKI, D. R., J. S. PEVNICK & J. D. GRIFFITH. 1978. Human pharmacology and abuse potential of the analgesic buprenorphine. Arch. Gen. Psychiatry **35:** 501–516.
25. MELLO, N. K., M. P. BREE & J. H. MENDELSON. 1981. Buprenorphine self-administration by rhesus monkey. Pharmacol. Biochem. Behav. **15:** 215–225.
26. SPITZER, R. L., J. ENDICOTT & E. ROBINS. 1978. Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders. 3rd edit. New York Biometrics Research, New York State Psychiatric Institute. New York.
27. LORR, M., C. J. KLETT, D. M. MCNAIR & J. J. LASKY. 1962. Inpatient Multidimensional Psychiatric Scale. Consulting Psychologists Press. Palo Alto, CA.
28. HAMILTON, M. 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiat. **23:** 56–62.
29. EMRICH, H. M., C. CORDING, S. PIRÉE, A. KÖLLING, D. v. ZERSSEN & A. HERZ. 1977. Indication of an antipsychotic action of the opiate antagonist naloxone. Pharmakopsychiatr/Neuro-Psychopharmakol. **10:** 265–270.
30. BRENGELMANN, J. C. 1959. The Effect of Repeated Electroshock on Learning in Depressives. Springer, Berlin-Göttingen-Heidelberg.
31. WEINER, R. D. 1979. The psychiatric use of electrically induced seizures. Am. J. Psychiatry **136:** 1507–1517.