Pharmacology Biochemistry & Behavior Vol 27, pp 525–527 © Pergamon Journals Ltd , 1987 Printed in the U S A 0091-3057/87 $3 00 + 00

BRIEF COMMUNICATION

Chronic Opioid Antagonist Treatment Facilitates Nonopioid, Stress-Induced Analgesia

BYRON C YOBURN,* LORI S TRUESDELL,† BENJAMIN KEST,† CHARLES E INTURRISI* AND RICHARD J BODNAR†

**Department of Pharmacology, Cornell University Medical College 1300 York Avenue, New York, NY 10021 and †Department of Psychology, Queens College of the City University of New York Flushing, NY 11367*

Received 27 October 1986

YOBURN, B C , L S TRUESDELL, B KEST, C E INTURRISI AND R J BODNAR *Chronic opioid antagonist treatment facilitates nonopioid, stress-induced analgesia* PHARMACOL BIOCHEM BEHAV 27(3) 525–527, 1987 — Chronic exposure to opioid antagonists produces increased brain opioid receptors and enhances morphine analgesia Since opioid antagonists could affect both opioid and nonopioid analgesic systems, the present study evaluated whether chronic opioid antagonist treatment with naltrexone alters the nonopioid analgesia produced by cold-water swims (CWS) Rats were implanted (SC) with two, 30 mg naltrexone pellets The pellets were removed 8 days later or left in place and rats tested 24 hr later for analgesia (tail-flick) following a 3 5 min CWS or morphine (3 mg/kg, SC) As expected, morphine analgesia was potentiated in rats with naltrexone pellets removed, but was blocked in rats tested with the naltrexone still implanted In contrast, naltrexone pretreatment potentiated CWS analgesia, irrespective of whether the pellets were removed or left in place These findings confirm the nonopioid nature of CWS analgesia and indicate that chronic treatment with an opioid antagonist can affect both opioid and nonopioid analgesic mechanisms

Chronic naltrexone treatment Cold-water swim analgesia Morphine analgesia Supersensitivity Rats

Chronic exposure to opioid antagonists produces an increase in brain opioid receptors (e g , [3, 6, 8, 10]) and an increase in the analgesic and toxic potency of morphine [5, 6, 8, 10] However, the increased potency of analgesic agents is not confined to opiate drugs Amir and Amit [1] have shown that opioid-mediated stress-induced analgesia elicited by inescapable, intermittent footshock is also enhanced following chronic treatment with the opioid antagonist naltrexone Since the analgesic responses induced by stressors have proved useful in elucidating endogenous mechanisms of opioid-mediated and nonopioid-mediated forms of pain-inhibition (see reviews [2,7]), and since opioid antagonists can affect both opioid and nonopioid systems [4], the present study evaluated whether chronic naltrexone treatment alters the nonopioid analgesic response following cold-water swims (CWS) CWS analgesia does not develop cross-tolerance with morphine analgesia, and is not significantly affected by naloxone [2]

The present study compared changes in CWS analgesia and morphine analgesia following implantation of naltrexone pellets over 8 days The pellets were either removed 24 hr prior to analgesic testing or left in place during analgesic testing Although receptor upregulation will occur in both conditions, functional supersensitivity to morphine analgesia will only be observed when the naltrexone pellets are removed [9] To determine whether the implantation protocols altered the stressful properties of CWS, a second physiological measure, CWS hypothermia was also assessed

METHOD

Subjects

Male albino Sprague-Dawley rats (300–500 g) were housed in pairs in wire mesh cages with free access to food and water Each rat was tested for baseline tail-flick latencies using a radiant heat source (IITC Tail Flick Analgesia Meter) mounted 8 cm above the tail and applied 3–6 cm proximal to the tip (baseline tail-flick latency=2–3 sec) Trials were terminated if a response did not occur within 10 sec and a 10 sec latency was recorded Each subject data point was the mean of three trials spaced 15 sec apart

CWS Protocol

Fifty-five rats were implanted subcutaneously with either

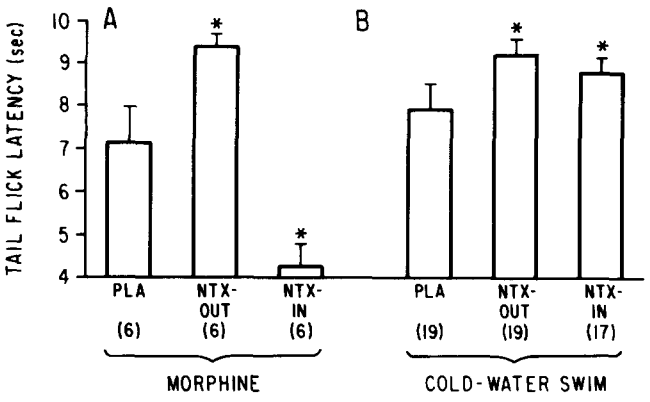

FIG 1 A Mean (+SEM) tailflick latency 60 min following 3 0 mg/kg morphine, SC B Mean (+SEM) tailflick latency 30 min following a 3 5 min cold-water swim PLA=combined placebo groups NTX-OUT=rats tested 24 hr following removal of naltrexone pellets NTX-IN=rats tested with the naltrexone pellets still implanted *=Significantly different from corresponding placebo control ($p<0$ 01) by 2-tailed post hoc t-test The number in parentheses indicates the N per group

two placebo pellets (n=19) or two naltrexone pellets (n=36) under light halothan anesthesia Naltrexone pellets (30 mg naltrexone, 105 mg cholesterol, 15 mg tristearin) and placebo pellets (135 mg cholesterol, 15 mg tristearin) were wrapped in nylon mesh prior to implantation to permit simplified removal as described previously [9] Eight days following implanation, pellets were either removed (NTX-OUT n=19, placebo n=9) under halothane anesthesia or left in place (NTX-IN n=17, placebo n=10) Nine days following implantation, each rat received a 3 5 min swim in a 2°C bath with tail-flick latencies determined prior to and 30 min following CWS Core body temperature, determined rectally by a digital thermometer (Bailey Instruments, accuracy=0 1 °C), was evaluated prior to and 30 min after CWS in placebo (n=14), NTX-OUT (n=13) and NTX-IN (n=13) groups In all experiments, the observer conducting the protocols was uninformed as to the pretreatment of each rat

Morphine Protocol

Eighteen additional rats were implanted with pellets which were either removed (NTX-OUT n=6, Placebo n=3) or left in place (NTX-IN n=6, Placebo n=3) eight days later Nine days following implantation, each rat received morphine sulfate (3 mg/kg, SC) with tailflick latencies determined prior to injection and 60 and 120 min after injection

Data Analysis

Data were evaluated using analyses of variance and post hoc comparisons as appropriate Latency data were converted to common log values prior to statistical analyses In order to compare the relative analgesia among treatment groups, latency data are also expressed as the percent of maximum possible effect (%MPE) (see [7])

RESULTS

Baseline Latencies

Tailflick latencies from baseline and experimental conditions of placebo-treated rats with pellets removed or left in place did not differ ($p>0$ 05) and these groups were combined (PLA) Baseline tailflick latencies prior to stress or morphine did not differ significantly ($p>0$ 05) among treatments (2 4, 2 3, 2 5 sec for PLA, NTX-OUT, NTX-IN, respectively)

Morphine Analgesia

Analysis of variance indicated a significant effect of treatment, time and a significant interaction between treatment and time, F's≥9 31, $p<0$ 001 Morphine significantly increased latencies in all groups at 60 and 120 min ($p<0$ 05) Removal of naltrexone pellets 24 hr earlier (NTX-OUT Group, MPE=91%) significantly enhanced (53% increase, $p<0$ 05) morphine analgesia compared to placebo (MPE=60%) treatment ($p<0$ 05) at 60 min following morphine administration (Fig 1A) In contrast, leaving the naltrexone pellets in place (NTX-IN Group, MPE=20%) significantly decreased (67% decrease, $p<0$ 05) morphine analgesia as compared to placebo (Fig 1A) Similar results were observed 120 min following morphine (data not shown)

CWS Analgesia

Analysis of variance indicated a significant effect of time and a significant interaction between treatment and time, F's≥3 78, $p<0$ 05 CWS significantly increased latencies in all groups ($p<0$ 05) Figure 1B illustrates the significant ($p<0$ 05) enhancement of CWS analgesia in the NTX-OUT (MPE=90%) and NTX-IN (MPE=84%) groups compared to placebo (MPE=73%), representing a 23% and 14% increase in analgesia, respectively, relative to placebo

CWS Hypothermia

Although significant hypothermia was observed between pre and post-swim conditions (F=810 13, $p<0$ 001), baseline core body temperatures (PLA 38 0, NTX-OUT 37 3, NTX-IN 37 9 °C) and 30 min post-swim temperatures (PLA 26 2, NTX-OUT 25 1, NTX-IN 24 7°C) failed to differ significantly ($p>0$ 05) among groups

DISCUSSION

The present data confirm that chronic naltrexone treatment produces functional supersensitivity (53% increase) to morphine analgesia if the pellets are removed at the end of dosing [5, 6, 8, 10], and that morphine analgesia is reduced by 67% in rats chronically treated with naltrexone and tested with the pellets still implanted [9] CWS analgesia is significantly enhanced by chronic naltrexone treatment irrespective of whether the naltrexone pellets are removed (23% increase) or left in place (14% increase) The enhancement of CWS analgesia cannot be attributed to any concomitant changes in CWS hypothermia

The failure of chronic naltrexone to block CWS analgesia confirms its essential nonopioid nature and agrees with the failure of acute naloxone or chronic morphine treatment to affect CWS analgesia [2] Curiously, the naltrexone-induced enhancement of CWS analgesia is unresponsive to opioid blockade, as evidenced by the similar analgesic response in the NTX-IN and NTX-OUT groups While it is possible that a higher challenge dose of naltrexone or other opioid antagonist might have eliminated the enhanced analgesic response following chronic naltrexone, the present dose of naltrexone produces a 50-fold rightward shift in the dose-response function for morphine analgesia [9] Therefore, it

appears that chronic naltrexone treatment may have exerted effects upon a nonopioid system which is consistent with previous suggestions that opioid antagonists have been shown to possess activity in several nonopioid systems [4]

ACKNOWLEDGEMENTS

This study was supported in part by NIDA Grants DA-01457 and DA-04185 (BCY and CEI) and NIH BRSG RR07064 (R J B) We thank Dr M T Turnock for her assistance

REFERENCES

1 Amir, S and Z Amit Enhanced analgesic effects of stress following chronic administration of naltrexone in rats *Eur J Pharmacol* **59** 137–140, 1979
2 Bodnar, R J , D D Kelly, M Brutus and M Glusman Stress-induced analgesia neural and hormonal determinants *Neurosci Biobehav Rev* **4**· 87–100, 1980
3 Lahti, R A and R J Collins Chronic naloxone results in prolonged increases in opiate binding sites in brain *Eur J Pharmacol* **51** 185–186, 1978
4 Sawynok, J , C Pinsky and F S LaBella Minireview on the specificity of naloxone as an opiate antagonist *Life Sci* **25** 1621–1632, 1979
5 Tang, A H and R J Collins Enhanced analgesic effects of morphine after chronic administration of naloxone in the rat *Eur J Pharmacol* **47** 473–474, 1978
6 Tempel, A , E L Gardner and R S Zukin Neurochemical and functional correlates of naltrexone-induced opiate receptor upregulation *J Pharmacol Exp Ther* **232** 439–444, 1985
7 Watkins, L R and D J Mayer Organization of endogenous opiate and nonopiate pain control systems *Science* **216** 1185–1192, 1982
8 Yoburn, B C , R R Goodman, A H Cohen, G W Pasternak and C E Inturrisi Increased analgesic potency of morphine and increased brain opioid binding sites in the rat following chronic naltrexone treatment *Life Sci* **35**. 2325–2332, 1985
9 Yoburn, B C , A H Cohen and C E Inturrisi Pharmacokinetics and pharmacodynamics of subcutaneous naltrexone pellets in the rat *J Pharmacol Exp Ther* **237**· 126–130, 1986
10 Yoburn, B C , F A Nunes, B Adler, G W Pasternak and C E Inturrisi Pharmacodynamic supersensitivity and opioid receptor upregulation in the mouse *J Pharmacol Exp Ther* **239**· 132–135, 1986