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Potentiation of Opiate Analgesia and Apparent Reversal of Morphine Tolerance by Proglumide

Abstract. *Exogenous cholecystokinin selectively antagonizes opiate analgesia, which suggests that endogenous cholecystokinin may act physiologically as an opiate antagonist and may play a role in opiate tolerance. The use of the selective cholecystokinin antagonist proglumide provided a test of these hypotheses in rats that were either inexperienced with or tolerant to opiates. Proglumide potentiated analgesia produced by morphine and endogenous opiates and seemed to reverse tolerance. These results suggest that endogenous cholecystokinin systems oppose the action of opiates.*

Cholecystokinin (CCK) selectively acts as an opiate antagonist in rats when administered either systemically or centrally (*1*). These findings, plus the finding of CCK in neural areas previously implicated in pain modulation (*2*), led us to hypothesize that endogenous CCK may function physiologically to oppose the analgesic effects of opiates. These data also suggest that tolerance resulting from repetitive opiate administration may be due to a compensatory increase in the activity of CCK systems. We tested these hypotheses by examining the effect of proglumide, a competitive CCK receptor antagonist (*3*), on opiate analgesia produced in rats either naïve to or tolerant of opiates.

We found that endogenous CCK functions physiologically as an opiate antagonist and plays a role in opiate tolerance. The observation that proglumide can potentiate opiate analgesia has implications for the administration of narcotics for both acute and chronic pain.

We initially examined the effect of five doses of proglumide (0.001, 0.01, 0.1, 1, and 5 μg) delivered intrathecally onto the lumbosacral cord (*4*) on analgesia (*5*) produced by intrathecally administered morphine (1 μg in 0.5 μl saline). Proglumide or equivolume vehicle [0.5 μl of 0.4 percent dimethyl sulfoxide (DMSO) and buffer] (*6*) was injected 10 minutes before and again immediately before morphine administration. A biphasic dose-response function was observed. Dose-related potentiation was produced by 0.001- and 0.01-μg doses (Fig. 1A), no effect by 0.1 μg, and dose-related attenuation by 1.0 and 5.0 μg (*7–9*).

Since these results suggest that endogenous CCK was able to oppose the antinociceptive actions of intrathecal morphine, we tested whether endogenous CCK might also attenuate analgesia induced by endogenous opiates. We examined the effect of 0.01 μg of proglumide (two intrathecal injections, 10 minutes apart) on analgesia produced by spinal release of endogenous opiates (front-paw footshock-induced analgesia) (*10*) and on

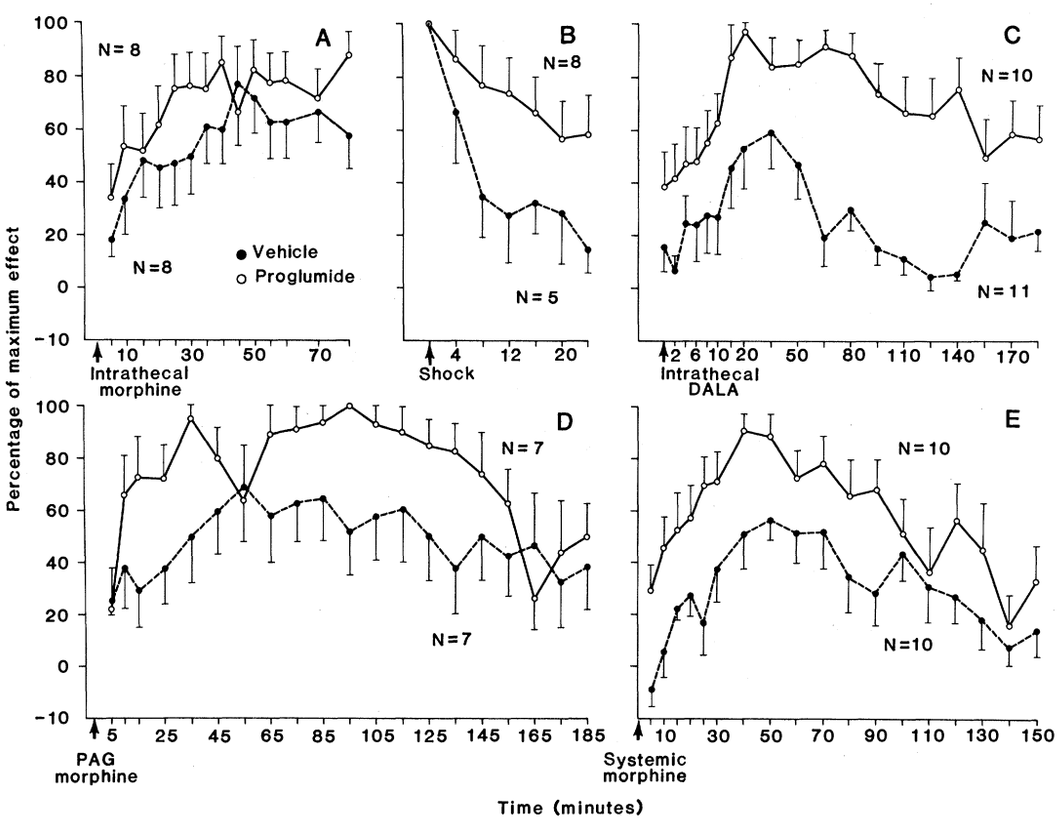

Fig. 1. Potentiation (mean ± standard error) of opiate analgesia by proglumide (two injections of 0.01 μg, the optimum potentiating dose). (A) Enhancement of intrathecal morphine analgesia by intrathecal proglumide. (B) Enhancement of front-paw footshock-induced analgesia by intrathecal proglumide. (C) Enhancement of intrathecal DALA analgesia by intrathecal proglumide. (D) Enhancement of PAG morphine analgesia by PAG proglumide. (E) Enhancement of systemic morphine analgesia by systemic proglumide. Data were evaluated by analyses of variance; for each comparison, $P < 0.0001$.

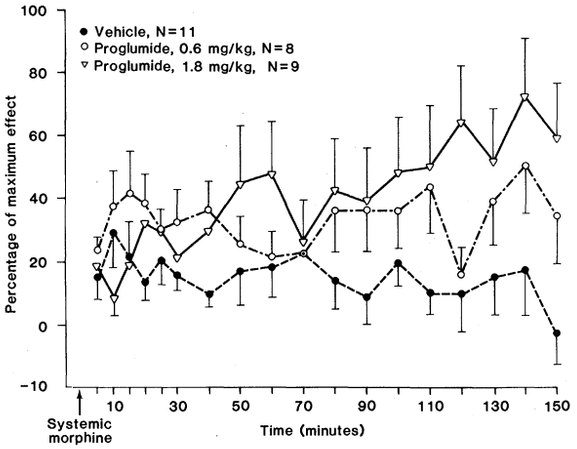

Fig. 2. Apparent antagonism of morphine tolerance by proglumide. Values are means ± standard errors. Both proglumide doses significantly enhanced analgesia in comparison with vehicle controls ($P < 0.0001$).

the analgesia produced by the stable enkephalin analog [D-Ala^2]methionine enkephalinamide (DALA; 3 μg in 0.5 μl saline, intrathecal). In both cases, proglumide markedly potentiated analgesia (Fig. 1, B and C).

We then examined whether the ability of CCK to antagonize opiate analgesia was unique to spinal circuitry. Since the periaqueductal gray (PAG) contains both opiate and CCK receptors (*2, 11*), we examined the effect of 0.01 μg of proglumide on 3 μg of morphine in 0.4 percent DMSO-saline (0.5 μl) after simultaneous microinjection (*4*) into PAG sites sensitive to morphine. Proglumide again potentiated morphine analgesia (Fig. 1D), (i) indicating that opiate-CCK interactions occur supraspinally as well as spinally and (ii) indicating that, in general, opiate actions are modulated by CCK systems.

If CCK antagonists are to be of clinical value they should be effective after systemic administration. We therefore examined the effect of systemic proglumide (0.002, 0.02, and 0.2 mg/kg in 1.2 percent DMSO-buffer, injected intraperitoneally) delivered 10 minutes and again just before a 3 mg/kg intraperitoneal injection of morphine. At a dose of 0.02 mg/kg, proglumide significantly potentiated morphine analgesia (Fig. 1E); 0.002 mg/kg produced a brief period of potentiation, and 0.2 mg/kg had no effect (*9, 12*).

These data show that proglumide can hasten the onset (Fig. 1, A, C, D, and E), increase the peak level (Fig. 1, C, D, and E), or prolong the duration (Fig. 1, B and C) of analgesia. These observations raise the possibility that administration of CCK antagonists could decrease the dose of narcotics necessary to relieve pain (*8*) and could enhance the effects of procedures such as acupuncture, which are mediated by endogenous opiates (*13*). Because our control studies showed that proglumide does not produce analgesia in the absence of opiates (*9*), these data imply that CCK systems are not tonically active but are activated in response to administration or release of opiates. This possibility suggests that the balance of activity between CCK and opiate systems may determine the level of pain sensitivity experienced by the organism.

Since (i) the phenomenon of opiate tolerance is observed at the behavioral level as a decrease in the efficacy of opiates to produce analgesia and (ii) endogenous CCK is able to effect such a decrease, CCK may play an important role in tolerance. Long-term opiate administration may induce a compensatory increase in CCK synthesis or release, which could result in a progressive antagonism of opiate analgesia.

We therefore examined whether systemic proglumide could attenuate morphine tolerance in rats. Tolerance was produced by a 6-day schedule of twice-daily intraperitoneal injections of increasing doses of morphine, culminating in 300 mg/kg on the final day (*14*). Upon completion of this regimen, rats were intraperitoneally injected with 0.6 or 1.8 mg of proglumide per kilogram or equivolume vehicle (1 ml of 1.2 percent DMSO-buffer per kilogram) 10 minutes and again just before an intraperitoneal injection of morphine (4 mg/kg which produces potent analgesia in naïve animals). A fourth group ($N = 10$) received two injections of vehicle followed by saline (morphine vehicle). The rats treated with vehicle plus morphine were not significantly more analgesic than those treated with vehicle plus saline; that is, they exhibited tolerance to the analgesic effects of morphine. In contrast, systemic coadministration of proglumide and morphine potentiated morphine analgesia (Fig. 2) (*9*).

These data show that proglumide can potentiate morphine analgesia in tolerant rats—that is, it can antagonize opiate tolerance (*15*). The data support the hypothesis that tolerance may develop, at least in part, from a progressive compensatory increase in the activity of CCK systems in response to prolonged opiate administration. If so, these results suggest that blockade of the CCK systems involved in pain modulation by drugs such as proglumide could potentially reverse or prevent the development of narcotic tolerance in patients with chronic pain.

L. R. WATKINS*
I. B. KINSCHECK
D. J. MAYER

Department of Physiology and Biophysics, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298

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6. Dimethyl sulfoxide was required to solubilize the proglumide. The buffer used was 0.05*M* phosphate, *p*H 7.4.
7. A biphasic dose-response curve is in accord with the observation that specific doses of CCK antagonize (*1*), have no effect on (*1*), or produce analgesia [G. Zetler, *Neuropharmacology* **19**, 415 (1980)].
8. In humans, intravenous administration of 50 μg of proglumide in combination with 4.2 mg of morphine per 70 kg of body weight produced a more potent and long-lasting analgesia than that produced by 5.6 mg/70 kg intravenous morphine alone. Administration of 100 μg of proglumide did not affect analgesia (D. D. Price, paper presented at the American Pain Society meeting, Chicago, November 1983).
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* Present address: Department of Animal Physiology, University of California, Davis 95616.

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