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The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia

Fabrizio Benedetti *

Department of Neuroscience and CIND Center for the Neurophysiology of Pain, University of Torino, Torino (Italy)

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Summary Discovery of the involvement of endogenous opiates in placebo analgesia represents an important step in understanding the mechanisms underlying placebo response. In the present study, we investigated the effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia in a human model of experimentally induced ischemic pain. First, we found that part of the placebo response was reversed by naloxone, confirming previous studies on the role of opioids in the placebo phenomenon. Second, since it was demonstrated that the action of exogenous and endogenous opiates is potentiated by proglumide, we analysed the effects of this cholecystokinin antagonist on placebo response and found that it enhanced placebo analgesia. The placebo effect can thus be modulated in two opposite directions: it can be partially abolished by naloxone and potentiated by proglumide. The fact that placebo potentiation by proglumide occurred only in placebo responders, but not in non-responders, suggests that activation of an endogenous opiate system is a necessary condition for the action of proglumide. These results suggest an inhibitory role for cholecystokinin in placebo response, although the low affinity of proglumide for cholecystokinin receptors does not rule out the possibility of other mechanisms.

Key words: Opiate; Naloxone; Cholecystokinin; Proglumide; Placebo analgesia; Pain

Introduction

The placebo phenomenon has always been considered in the medical literature as a control condition in pharmacological studies (Ross and Buckalew 1985; Wilkins 1985) as well as a potential therapeutic tool (Rawlinson 1985). In particular, placebo analgesia represents a situation where the administration of a substance known to be non-analgesic (e.g., saline solution) produces an analgesic response when the patient strongly believes that pain will disappear.

The biology of placebo was born when some authors discovered that placebo analgesia is mediated by endogenous opiates. This claim came from the observation that the opiate antagonist naloxone is capable of reversing placebo analgesia (Levine et al. 1978; Grevert et al. 1983; Fields and Levine 1984; Levine and Gordon 1984). However, a non-opioid component in the placebo response was also found (Gracely et al. 1983). The endogenous opiates interact with other neuropeptides in the central nervous system (CNS). In particular, in the last years attention focused on cholecystokinin (CCK). In fact, CCK is a recognized neurotransmitter of the CNS (Vanderhaegen et al. 1975; Beinfeld 1983) with a distribution matching that of the opioid peptides such as enkephalin, β-endorphin and dynorphin (Stengaard-Pedersen and Larsson 1981; Gall et al. 1987; Gibbins et al. 1987). From a functional viewpoint, CCK inhibits the analgesic effects of morphine (Faris et al. 1983), β-endorphin (Itoh et al. 1982) and electroacupuncture (Han et al. 1986). By contrast, the administration of the CCK receptor antagonist proglumide potentiates the analgesic effects of morphine (Watkins et al. 1985b), β-endorphin (Katsuura and Itoh 1985) and enkephalin (Watkins et al. 1985a). In addition, two studies performed in human subjects showed that proglumide enhances morphine analgesia

* *Corresponding author:* Fabrizio Benedetti, Dipartimento di Neuroscienze, Università di Torino, Corso Raffaello 30, 10125 Torino, Italy. Tel.: (39) 11-670-77-09; FAX: (39) 11-670-77-08.

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in experimental (Price et al. 1985) and clinical pain (Lavigne et al. 1989), although Lehmann et al. (1989) did not find any effect of proglumide. All these data suggest that CCK acts as a physiologic antagonist of opiates (see Baber et al. 1989 for a review). On the basis of these considerations, we decided to study the effects of different doses of proglumide on placebo analgesia; our rationale was that, if placebo analgesia is mediated by opioids, a potentiation of the placebo response by proglumide should be found.

Methods

Pain was induced experimentally by means of the submaximum effort tourniquet technique (Smith et al. 1966, 1972). The subject reclined on a bed; his/her left forearm was extended vertically and venous blood was drained through an Esmarch bandage. A sphygmomanometer cuff was then placed around the upper arm and inflated to a pressure of 250 mm Hg. After this, the bandage was suddenly removed and the arm lowered on the subject's side. Then, after 1 min, the subject started squeezing a hand exerciser 12 times every 2 sec. The force necessary to bring the handles together was 6.5 kg. This type of ischemic pain increases over time (Smith et al. 1966,

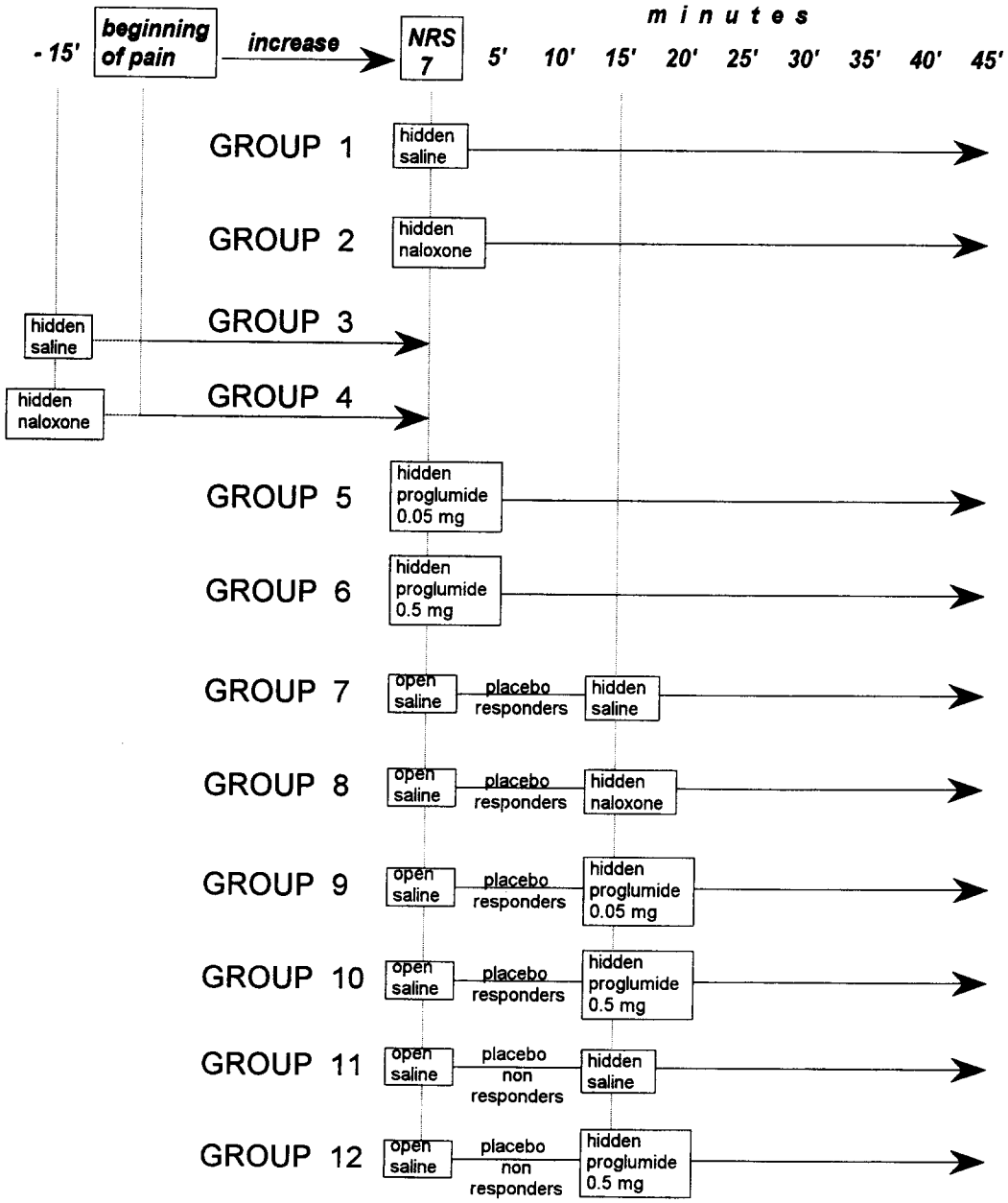

Fig. 1. Experimental design for each group of subjects. Starting from a pain intensity numerical rating scale (NRS) of 7 (time 0), the experimental conditions differed for each group. Subjects scored pain intensity every 5 min up to 45 min. Groups 3 and 4 represent special cases where pain intensity was scored from the beginning of pain to NRS = 7.

1972). The subject judged pain intensity according to a numerical rating scale (NRS) placed in front of her/him. This consisted of numbers from 0 to 10; at the 0 edge 'no pain' was indicated, and at the 10 edge 'unbearable pain' was specified. In order to have the same pain intensity baseline in all subjects, the experiment started when the subject scored 7. When the score reached 10 the experiment was discontinued.

Before starting the procedure described above, a needle was inserted into a vein of the right forearm. The needle was connected to a line, 1 m long, through which a slow infusion of 5% glucose solution was administered. The intravenous line reached an adjacent room where hidden injections could be performed by the experimenter. In such a way, either injections in full view of the subject or hidden injections could be made.

The experiments were performed according to a double-blind procedure on 340 healthy volunteers (154 male, 186 female) ranging from 19 to 51 years of age, whose consent was previously obtained; they were informed about the experiment and the possible use of naloxone and proglumide.

The first 117 subjects were randomly subdivided into 6 control groups. The experimental design for each group is shown in Fig. 1. Group 1 (67 subjects) was defined the 'natural history' or 'no-treatment' group and was used to furnish data on the normal changes in pain ratings; in this group, when subjects reached 7 on the NRS, a hidden injection of saline (0.9% NaCl) was made. Usually, a placebo response is not defined as the response of an individual, but as a group effect. Instead, in the present study we defined a subject as a placebo responder when pain rating was 7 or less at 15 min following the open saline injection. Therefore, 67 subjects were randomly assigned to group 1 in order to demonstrate that it is safe to define a placebo responder in this way. Group 2 (10 subjects) was defined the 'hidden naloxone' group and was used to see whether naloxone (10 mg) itself produced an increase of pain; in this group, a hidden injection of naloxone was made at NRS = 7. Groups 3 (control, 10 subjects) and 4 (naloxone, 10 subjects) were used to monitor the possible effects of naloxone at low levels of pain intensity. A hidden injection of either saline (group 3) or 10 mg of naloxone (group 4) were performed 15 min before the beginning of pain, and pain rating lasted until NRS = 7 was reached. Groups 5 (10 subjects) and 6 (10 subjects) were called 'hidden proglumide' groups and were used to see whether proglumide (group 5 = 0.05 mg; group 6 = 0.5 mg) itself produced a decrease of pain; in these groups, a hidden injection of proglumide was made at NRS = 7.

In order to obtain 60 placebo responders, the remaining 223 subjects received an injection of saline in full view (placebo) when NRS = 7 was reached. If pain rating was 7 or less at 15 min following the open saline injection, a subject was considered a placebo responder (see also Results). In the 60 responders (26.9%), the experimental procedure continued randomly according to groups 7, 8, 9 or 10. Group 7 (15 subjects) was defined the 'placebo-saline' group; in this group, when subjects reached 7 on the NRS, an injection of saline in full view of the subject (placebo) was performed. The subject was told that the injected substance was a very potent painkiller acting very quickly within 20 min. After 15 min from the placebo injection, a hidden injection of saline was performed, for comparison with groups 8, 9 and 10. Group 8 (15 subjects) was defined the 'placebo-naloxone' group; in this group, when subjects reached 7 on the NRS, an injection of saline in full view (placebo) was performed. As in group 7, the subject was told that the substance was a potent painkiller acting within 20 min. After 15 min from placebo injection, thus 5 min before the expected maximum placebo effect, a hidden injection of naloxone (10 mg) was performed. Groups 9 (15 subjects) and 10 (15 subjects) were called 'placebo-proglumide' groups and were the same as group 8 but, after 15 min from the placebo injection, a hidden injection of proglumide (group 9 = 0.05 mg; group 10 = 0.5 mg) was made.

Most of the subjects (163 of 223) did not respond to the placebo. A non-responder was defined as a subject with a pain rating of 8 or more at 15 min from the placebo injection; 30 of these 163 subjects were randomly chosen on the basis of previously assigned numbers, and represented groups 11 and 12. Group 11 (15 subjects) was defined the 'non-responder saline' group and was used as a control for comparison with group 12; the procedure was the same as in groups 7, 8, 9, 10 but a hidden injection of saline was made in placebo non-responders. Group 12 (15 subjects) was called the 'non-responder proglumide' group and was used to see whether proglumide was effective in placebo non-responders; the procedure was the same as in group 11 but a hidden injection of proglumide (0.5 mg) was made in non-responders after 15 min from the placebo injection.

It is very important to point out that the subjects of groups 1, 2, 3, 4, 5, 6 did not know that any injection was performed, whereas the subjects of groups 7, 8, 9, 10, 11, 12 were only aware of the first injection (placebo). Starting from the first score of 7, the subjects scored, according to the NRS, every 5 min. After 45 min from the first injection, the experiment was discontinued even if pain ratings were still low. In fact, by considering these 45 min plus the waiting time to reach NRS = 7, the experiment lasted more than 1 h. After this time, subjects reported to be tired and usually asked to discontinue the experiment even if their pain was not rated as unbearable. Analogously, subjects of groups 3 and 4 scored every 5 min, from the last squeezing to NRS = 7.

The differences between and within treatments were tested by means of the analysis of variance (ANOVA) followed by the Newman-Keuls' multiple range test for multiple comparisons. In addition, the differences between groups 7, 8, 9 and 10 were estimated by means of the area under the curve (AUC) calculated by the triangulation method (Winter and Flataker 1949). Data are presented as mean and SEM. Differences were considered to be statistically significant at $P < 0.05$.

Results

Although the time to reach NRS = 7 from the beginning of ischemic pain varied across subjects within the same group, we found no difference among different groups (except groups 3 and 4), as shown in Table I. By observing the standard deviations it is possible to see that, though the intervals ranged across subjects from less than 20 min to more than 30 min, the mean

Table I

MEAN TIME (minutes ± SD) TO REACH NRS = 7 FROM THE BEGINNING OF ISCHEMIC PAIN FOR EACH GROUP

Group	Minutes (± SD)
1	25.75 ± 8.42
2	23.15 ± 4.63
3	32.50 + 6.77
4	34.50 + 4.97
5	23.85 ± 5.31
6	24.05 ± 6.31
7	23.45 ± 5.96
8	23.95 ± 6.12
9	24.15 ± 6.23
10	24.05 ± 5.15
11	25.15 ± 7.05
12	23.18 ± 6.10

time intervals were very similar in all groups ($F(9, 177) = 0.42$, $P = 0.92$). The same times needed to reach NRS = 7 in all groups make all the experimental treatments equal to each other, from the beginning of pain to the end of the experiment. However, groups 3 and 4 showed longer times, probably because of the different experimental conditions. In fact, whereas all the other groups started scoring from NRS = 7, these two groups scored every 5 min from the last squeezing to NRS = 7: this could have increased the delay of a few minutes.

In the natural history group (group 1), pain was always larger than 7 (mean = 8.7 ± 0.24 SEM) at 15 min following the hidden saline injection (made when the subjects reached NRS = 7). At this time, we never found subjects with pain rating of 7, showing that it is safe to define a placebo responder when NRS is still 7 or less after 15 min from the open saline injection.

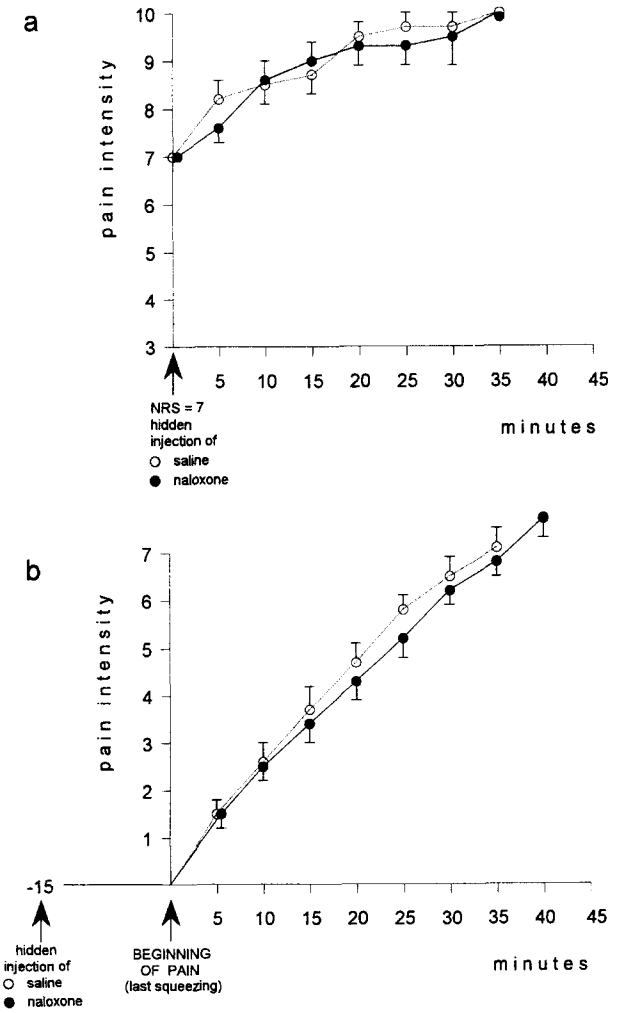

Fig. 2. (a) Comparison between hidden saline (group 1) and hidden naloxone (group 2), and (b) hidden saline (group 3) and hidden naloxone (group 4). In the first case, the possible effects of naloxone at NRS > 7 were tested, in the second case, the possible effects at NRS < 7 were tested. In all cases, no difference can be seen.

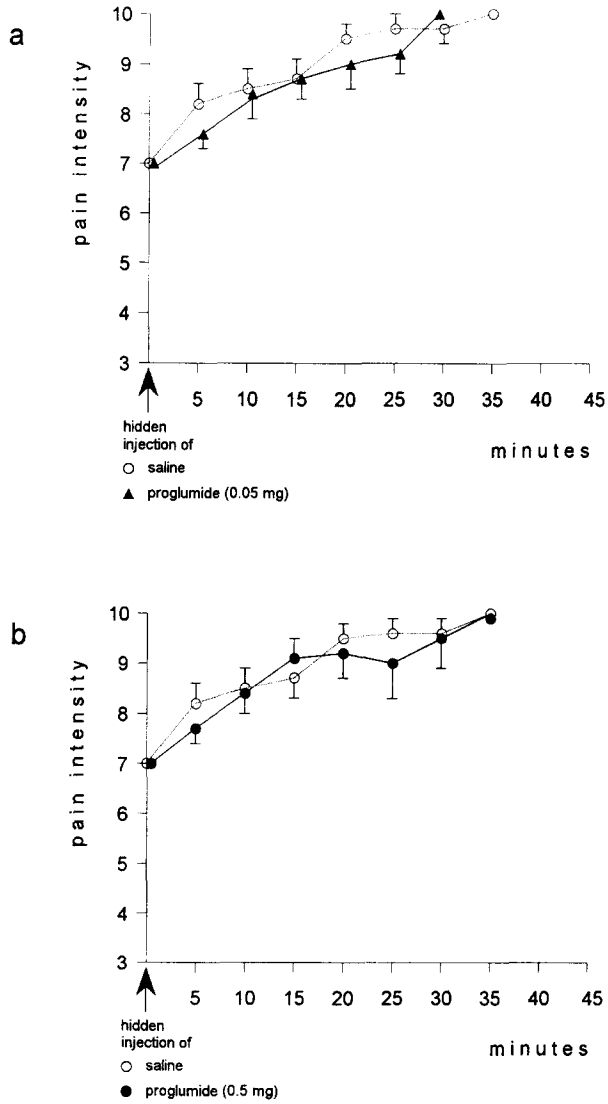

Fig. 3. Comparison between hidden saline (group 1), (a) hidden 0.05 (group 5) and (b) hidden 0.5 mg (group 6) of proglumide. No difference is present.

In order to study whether naloxone blocks and proglumide potentiates placebo response, we wanted to check for a possible hyperalgesic effect of naloxone and a possible analgesic effect of proglumide in our experimental conditions. Fig. 2a shows the comparison between the natural history group (○) and the hidden naloxone group (●). As already demonstrated previously (Grevert and Goldstein 1977, 1978), we found that naloxone did not increase this type of experimental pain with respect to the natural history group. In both cases, pain significantly increased over time ($F(7, 66) = 14.15$, $P < 0.001$ for group 1, and $F(7, 9) = 13.21$, $P < 0.001$ for group 2), but the two groups did not show any difference. In order to rule out the possibility of a hidden hyperalgesic effect due to the high pain intensity (NRS = 7), a hidden injection of naloxone (10 mg) was made 15 min before the beginning of pain

(group 4) and compared to a hidden injection of saline (group 3), as shown in Fig. 2b. It is possible to see that no difference was found between the two groups even at low levels of pain intensity (NRS < 7).

Analogously, Fig. 3 shows the comparison between the no-treatment group (○), the hidden proglumide 0.05 group (▲) and the hidden proglumide 0.5 group (●). Again, as already shown previously (Watkins et al. 1985a,b; Baber et al. 1989), we found that proglumide itself did not decrease this kind of experimental pain. In both proglumide groups, pain significantly increased over time ($F(6, 9) = 11.33$, $P < 0.001$ for group 5, and $F(7, 9) = 9.76$, $P < 0.001$ for group 6), and there was no difference relative to the no-treatment group. In all cases, NRS reached 10 at 30–35 min, and the experiments were thus discontinued.

When a saline injection into the intravenous line was performed in full view of the subjects (open injection), a strong placebo response could be elicited in 60 subjects (26.9%: see Methods). Group 7 was represented by 15 of these 60 placebo responders. The time course of the placebo analgesia in group 7 is shown in Fig. 4 (●) and compared to the natural history group (○). Group 7 showed a decrease of pain over time ($F(9, 14) = 13.43$, $P < 0.001$). The first significant difference relative to the natural history group appeared at 10 min (NRS of group 1 = 8.5 ± 0.24 SEM, and NRS of group 7 = 6.5 ± 0.25 SEM; $F(1, 80) = 14.64$, $P < 0.001$), increased at 15 min (NRS of group 1 = 8.7 ± 0.24 SEM, and NRS of group 7 = 6.1 ± 0.21 SEM; $F(1, 80) = 25.11$, $P < 0.001$), and was maintained up to 45 min (NRS of group 7 = 5.3 ± 0.3 SEM). The Newman-Keuls' multiple range test confirmed that the first significant decrease of pain occurred at 15 min relative to time 0 ($q = 3.781$, $P < 0.05$). Therefore, in these experimental conditions, a placebo effect occurred within 10–15 min. The Newman-Keuls' test also showed that a strong placebo effect was maintained at 45 min ($q = 6.698$, $P < 0.01$ relative to time 0). The hidden injection of saline was used as a control with respect to groups 8, 9, 10.

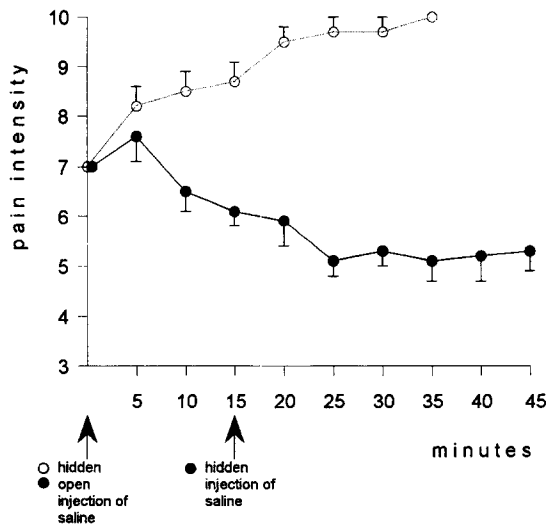

Fig. 4. Comparison between no-treatment (group 1; ○) and open saline (group 7). Note the strong placebo analgesic response.

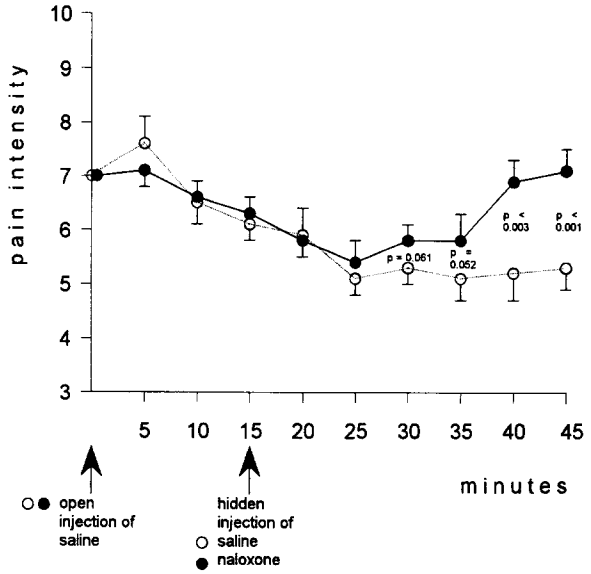

Fig. 5. Comparison between open saline – hidden saline (group 7; ○) and open saline – hidden naloxone (group 8). A clearcut reduction of the placebo analgesic response can be observed following naloxone injection.

The placebo response elicited by an open injection of saline could partially be reversed if a hidden injection of naloxone (10 mg) was performed at 15 min (Fig. 5). The hidden injection of naloxone produced a decrease of the placebo response, as shown by the significant differences at 40 min (NRS of group 7 = 5.2 ± 0.42 SEM, and NRS of group 8 = 6.9 ± 0.27 SEM; $F(1, 28) = 11.59$, $P < 0.003$) and 45 min (NRS of group 7 = 5.3 ± 0.3 SEM, and NRS of group 8 = 7.1 ± 0.34 SEM; $F(1, 28) = 15.76$, $P < 0.001$). It should be noted that difference is very close to significance at 30 and 35 min ($P = 0.061$ and $P = 0.052$, respectively). The Newman-Keuls' test showed that pain intensity of group 8 at 40 and 45 min did not differ relative to time 0 ($P = 0.994$ and $P = 0.999$, respectively).

The placebo response elicited by the open injection of saline could be potentiated by a hidden injection of 0.5 mg of proglumide but not by 0.05 mg (Fig. 6). The hidden injection of 0.05 mg of proglumide produced no different effect with respect to group 7 (Fig. 6a). By contrast, the hidden injection of 0.5 mg of proglumide at 15 min (Fig. 6b) potentiated the placebo analgesia at 35 min (NRS = 4.4 ± 0.18 SEM), 40 min (NRS = 4.1 + 0.23 SEM), and 45 min (NRS = 4.1 ± 0.37 SEM) ($F(1, 28) = 6.77$, $P < 0.02$, $F(1, 28) = 5.28$, $P < 0.03$, and $F(1, 28) = 6.35$, $P < 0.02$, respectively).

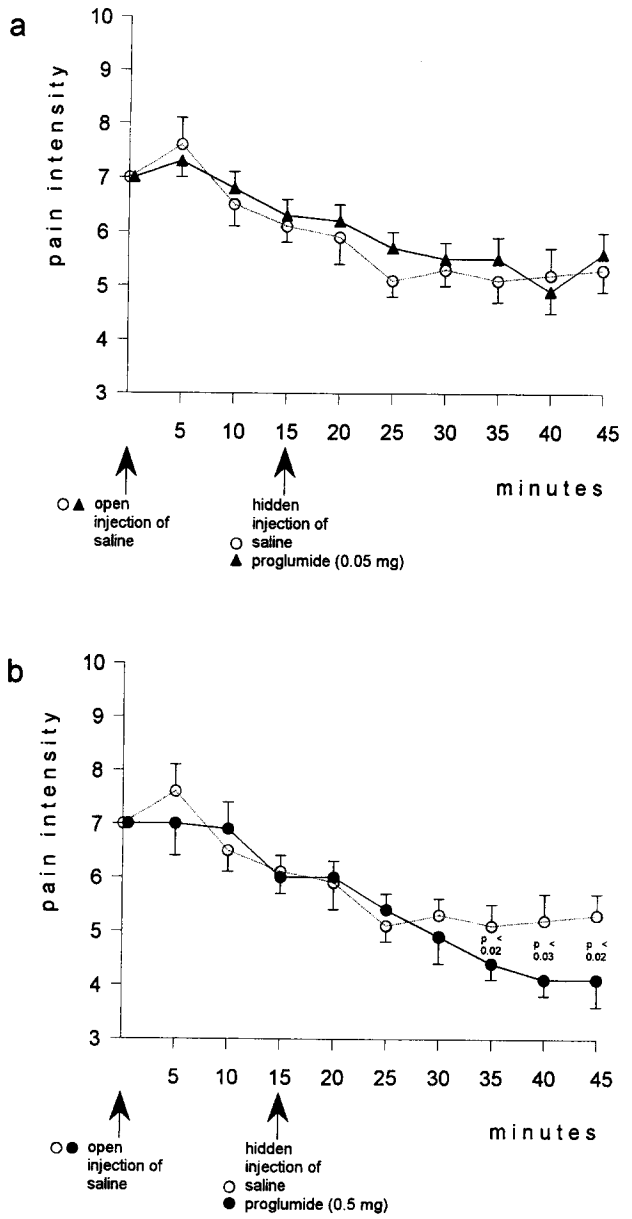

Fig. 6. Comparison between open saline – hidden saline (group 7; ○) and open saline – hidden proglumide ((a) group 9: 0.05 mg, and (b) group 10: 0.5 mg). A clear potentiation of the placebo analgesic response can be observed in (b) but not in (a).

The differences between groups 7, 8, 9 and 10, from time 0 (NRS = 7) to the end of the experiment at 45 min, are expressed as the AUC in Fig. 7. It is possible to see that AUC in the naloxone group (31.25 ± 5.05 SEM) was significantly smaller ($F(1, 28) = 9.35$, $P < 0.005$) than the control saline group (52.75 ± 4.89 SEM). By contrast, 0.5 mg of proglumide produced a AUC larger (64.25 ± 2.65 SEM) than the control ($F(1, 28) = 4.28$, $P < 0.05$). The group of 0.05 mg of proglumide (AUC = 45 ± 5.54 SEM) did not differ significantly from the control ($F(1, 28) = 1.1$, $P = 0.303$).

If 0.5 mg of proglumide were administered to placebo non-responders (group 12), no different effect

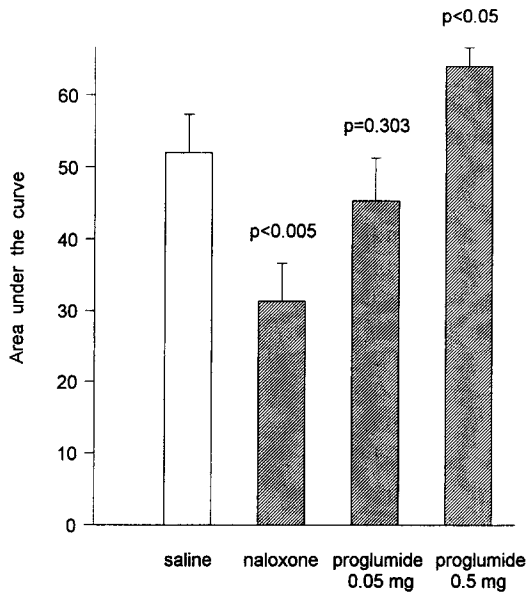

Fig. 7. Area under the curve for group 7 (saline), 8 (naloxone), 9 (proglumide 0.05 mg), and 10 (proglumide 0.5 mg), calculated from time 0 (NRS = 7) to the end of the experiment at 45 min. Each experimental group (shaded bars) is compared to the control group (white bar).

was observed with respect to the control (group 11), as shown in Fig. 8. The Newman-Keuls' multiple range test showed that a significant increase of pain intensity was present at 15 min in both groups (NRS of group 11 = 8.8 ± 0.17 SEM, and NRS of group 12 = 8.5 ± 0.21 SEM) with respect to time 0 ($q = 7.515$ for group 11 and $q = 6.345$ for group 12, $P < 0.01$), indicating that a placebo response did not occur. Following the hidden

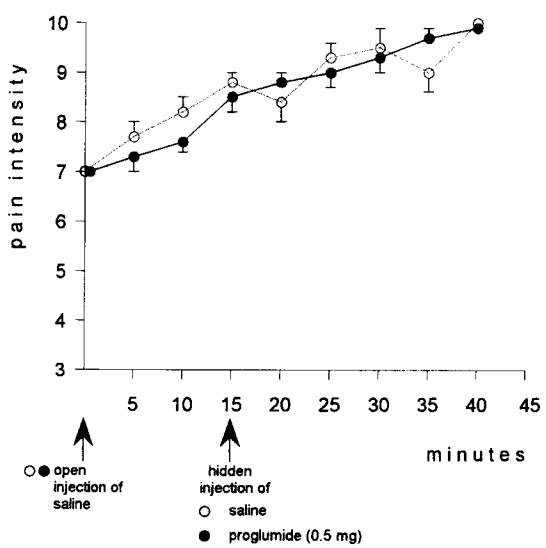

Fig. 8. Comparison between open saline – hidden saline (group 11) and open saline – hidden proglumide (0.5 mg) (group 12) in placebo non responders. No effect of proglumide was observed if placebo response was not present.

injection of either saline or proglumide, pain continued increasing in both groups up to NRS = 10, with no significant difference. At 35–40 min the experiments were discontinued.

Discussion

In order to compare the findings of the present work with previous studies, some methodological considerations can be made. According to Grevert and Goldstein (1985), in order to determine if a drug influences placebo response, several criteria must be included in the experimental design. First, a no-treatment control group, or natural history group, must be considered to monitor the natural course of pain and to verify if placebo really reduces pain. Second, a hidden-injection condition must be performed to demonstrate that the drug by itself does not influence pain. Third, different groups of subjects must be used to avoid for instance the attitude that the placebo does not work when naloxone is administered. Fourth, the appropriate dose of drug must be used. We included all these criteria, both for naloxone and proglumide, such that each experimental condition had its control counterpart. A natural history group was used to verify if a placebo effect was present, hidden injections were performed to determine if naloxone itself had hyperalgesic effects and if proglumide itself had analgesic effects, different groups of subjects were used, and finally a large dose of naloxone (10 mg) and two doses of proglumide (0.05 and 0.5 mg) were tested.

The experiments performed in groups 2, 4, 5 and 6 showed that naloxone and proglumide had no effect on this kind of experimental pain. Although clinical post-surgical pain was shown to be affected by naloxone (e.g., Lasagna 1965; Gracely et al. 1983), experimental ischemic arm pain (Grevert and Goldstein 1977, 1978), electric shock pain (El-Sobsky et al. 1976), and cold water pressor pain (Grevert and Goldstein 1978) are not influenced by doses of naloxone as high as 20 mg. Therefore, the results of the present study are in accordance with the notion that naloxone itself does not affect some kinds of experimental pain. Analogously, as already demonstrated by Price et al. (1985), Watkins et al. (1985a,b) and Kellstein and Mayer (1990), proglumide itself has no effect on pain.

By analysing a complex series of control and experimental groups, the present study demonstrates that the placebo analgesic response can be modulated in two opposite directions by using two different classes of drugs. The placebo phenomenon can be partially abolished by the opioid antagonist naloxone and potentiated by the CCK antagonist proglumide. The results obtained with 10 mg of naloxone are in accordance with and confirm the previous studies by Levine et al. (1978), Grevert et al. (1983), Levine and Gordon (1984), and Grevert and Goldstein (1985). In particular, the partial reversal of the placebo effect of the present study confirms the findings of Grevert et al. (1983), who also found a reduction, and not a complete abolition, of the placebo effect by naloxone. In fact, in our study we found that an analgesic effect was still present at 45 min, suggesting three possible conclusions: (1) a higher dose of naloxone could block the effect completely; (2) a non-opiate component could be involved; (3) a complete reversal could occur if more time was allowed. Although the present study cannot differentiate among these three possibilities, it shows that at least a part of placebo analgesia is mediated by endogenous opiates.

The potent antagonist action of naloxone on μ opioid receptors and the high affinity of β-endorphin for μ receptors (Paterson et al. 1983; Grevert and Goldstein 1985; Holaday et al. 1989) suggest a role for endorphins in placebo analgesia. However, it should be reminded that naloxone also shows a low affinity (10–20 times poorer) for δ and κ receptors and these opioid receptors bind leu-enkephalin and dinorphin A (Paterson et al. 1983; Grevert and Goldstein 1985). Since in the present study a high dose of naloxone (10 mg) was used, it is conceivable to hypothesize that μ, δ and κ opioid receptors resulted to be involved. Therefore, the present results can not differentiate which opioid peptides play a role in placebo analgesia.

As far as proglumide is concerned, the present results suggest that CCK has an inhibitory effect on the placebo response. However, although there is overwhelming behavioral and electrophysiological evidence that CCK is blocked by proglumide in the brain (Chiodo and Bunney 1983; Suberg et al. 1985; Watkins et al. 1985a,b), it should be reminded that proglumide has a low affinity for CCK receptors in the brain (Lin and Miller 1985; Wennogle et al. 1985a,b). Therefore, the action of proglumide may also be mediated by mechanisms other than blockade of CCK receptors. For example, proglumide could influence the bio-availability and metabolism of endogenous opiates or, otherwise, could act by influencing opioid binding to the receptors (Lavigne et al. 1989). Instead, if we assume that CCK is blocked by the systemic administration of 0.5 mg proglumide and that CCK acts as a physiologic antagonist of exogenous (Itoh et al. 1982; Faris et al. 1983) and endogenous opiates (Han et al. 1986), the potentiation of placebo analgesia by proglumide can be viewed as an evidence for the involvement of CCK in the placebo phenomenon. In other words, the blockade of CCK increased the effects of opioids released by the placebo procedure.

Because of this discrepancy between the behavioral-electrophysiological studies and the receptor studies regarding the action of proglumide, there is no

conclusive role for CCK in placebo analgesia. In any case, proglumide appears to have an important effect on placebo response. In particular, two points should be emphasized. First, the effects of proglumide occur only in placebo responders but not in non-responders, suggesting that the activation of an endogenous opioid system is a necessary condition for its action. This can be considered as a further evidence for a role of endogenous opiates in placebo analgesia. Reasoning in this way, analgesia potentiation by proglumide can be viewed as a probe for testing the involvement of an endogenous opiate system. Second, whereas proglumide potentiates analgesia mediated by D-alanine methionine enkephalinamide (μ and δ opioid receptor agonist), morphin (μ agonist), and β-endorphin (μ agonist), it fails to increase analgesia mediated by U-50,488H (a selective κ agonist) (Lord et al. 1977; Lavigne et al. 1989). This fact might suggest that dinorphin A plays a minor role in placebo analgesia, since it shows high affinity for κ receptors.

The opposite effects of opioid antagonists and CCK antagonists in placebo analgesia show that some of the intricate mechanisms underlying the linkage between mental activity and pain perception begin to be understood. This knowledge will be useful both for the understanding of higher brain functions and for the development of new therapeutic strategies aimed at potentiating the effects of the endogenous opiate systems.

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