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Naloxone-Sensitive Hyperalgesia Follows Analgesia Induced by Morphine and Environmental Stimulation

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HENDRIE, C. A. *Naloxone-sensitive hyperalgesia follows analgesia induced by morphine and environmental stimulation.* PHARMACOL BIOCHEM BEHAV **32**(4) 961–966, 1989.—Manipulations of attack parameters in murine agonistic encounters have shown that moderate attack terminating at the first unambiguous display of the upright submissive posture results in nonopioid analgesia. By contrast, attack continuing significantly beyond this behavioural marker results in decreases in nociception mediated by opioidergic mechanisms. However, these effects have only been demonstrated immediately upon termination of encounters. As such, little is known of the influences of agonistic encounters on nociceptive responding beyond this. Tail-flick latencies of male DBA/2 mice that had been exposed to opioid activating attack parameters were established at 15-minute intervals up to 90 min postattack. Data suggest the existence of at least two distinct phases in nociceptive responding with 1) analgesia being evident in the early phase (0–45 min) and 2) short-lasting (detectable only at 75 min postattack) hyperalgesia in the late phase. Further studies revealed both of these effects to be reversed by low (1–10 mg/kg) doses of naloxone. Interestingly, alterations in responsivity to noxious stimulation postmorphine (1–20 mg/kg) administration followed a similar pattern, with analgesia being detectable 0–2 hr and hyperalgesia being evident at 4 hr postinjection of either 10 or 20 mg/kg morphine. However, only the hyperalgesia induced by 20 mg/kg morphine was reversed by 10 but not 1 mg/kg naloxone. These data together suggest a relationship between the dose of morphine required to induce hyperalgesia and the amount of naloxone needed to reverse this response. The naloxone-reversibility of postencounter or morphine-induced hyperalgesia suggests that these effects are not a consequence of the absence of opiates/opioids per se. Rather, current data indicate these hyperalgesias to be mediated by the actions of a ligand acting upon opiate receptor mechanisms to produce effects opposite to those of traditional agonists. Current data do not allow firm conclusions to be drawn concerning the identity of this putative ligand, however, evidence does suggest that ACTH has many of the properties that such an opioid inverse agonist may be expected to possess.

Analgesia Hyperalgesia Environmentally-induced analgesia Opioid Opiate Naloxone Morphine

FOR well over a decade now, evidence has been amassing to suggest the existence of potent endogenous analgesia mechanisms. Further, as our understanding of this area has increased it has become apparent that such an analgesic system is multidimensional. For example, relatively minor alterations in stimulus parameters can induce analgesias that are differentially naloxone-sensitive, cross-tolerant with morphine and have variable time-courses. These have now been classified into hormonal or neural opioid or nonopioid (24,25).

Studies using more 'naturalistic' stimuli such as those that may be present within a resident-intruder paradigm have shown to a large extent that the various forms of analgesia outlined above may be demonstrated in response to the attentions of an aggressive conspecific. Exposure to a resident for 10 min (16) or to a specific number of attack bites (12,22) have been shown to activate central, opioid-mediated analgesia mechanisms. Interestingly, these variations in encounter criterion both involve attack continuing beyond the display of the upright submissive posture and it has been suggested that "loss of control" over the source of aversive stimulation (in this case, attack bites ensuing from the resident animal) may be of prime psychological importance for the display of opioid-mediated analgesias (16).

When encounters are terminated upon the first unequivocal display of the upright submissive posture, analgesia of a nonopioid form is induced (18). Further, this class of environmentally-induced analgesia is relatively short-lasting (<10 min) compared to the opioid form, whose duration is in the order of 45–60 min (17). Thus, whilst it has not as yet proved possible to determine with certainty the neural or hormonal mediation of these responses, they may be minimally differentiated into central or peripheral opioid and nonopioid. It is further apparent that whilst the nonopioid analgesia is precedent in temporal terms it is not an

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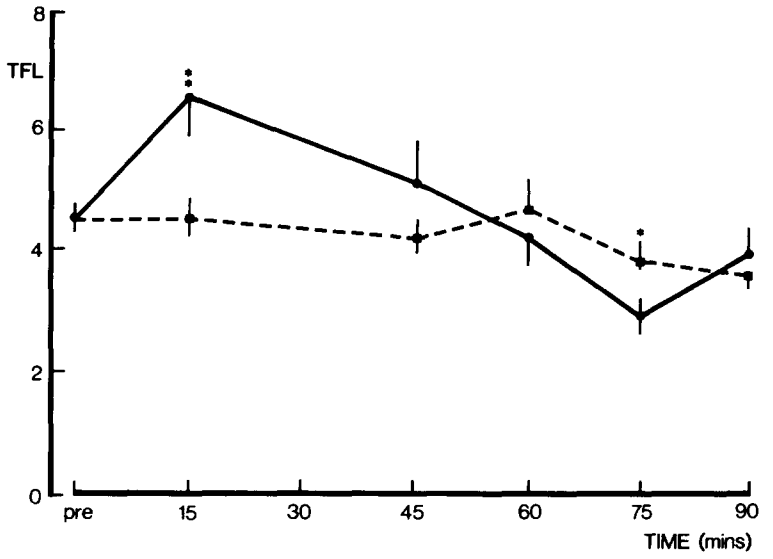

FIG. 1. Time course of agonistic encounter-induced alterations in nociception. Data are expressed as mean TFLs. The broken line indicates control responding, whilst the solid line represents the TFLs of male DBA/2 mice exposed to 35 attack bites beyond the first unambiguous display of the upright submissive posture. Analysis of the time course of nociceptive responding revealed the existence of at least two distinct phases, with analgesia being evident at 15 min and hyperalgesia at 75 min postencounter. See text for further details. $^{**}p<0.01$; $^{*}p<0.05$.

essential prerequisite for the expression of the opioid form (19).

To date, whilst much is known concerning the substrates mediating, and the stimulus parameters required to activate endogenous analgesia mechanisms, little is currently known concerning the adaptive significance of these responses. It has been suggested that the nonopioid form may be of benefit to an animal in situations where danger has been signalled through olfaction or some other means and where escape from that threat is possible (19). The opioid form, on the other hand, would confer advantage to an animal which is actively involved in defending itself from predatory or conspecific attack. In such a situation it would be clearly maladaptive for an animal to heed scratches and/or wounds incurred whilst engaging in what may potentially be a life or death struggle. Conversely, however, the *perception* of pain would be of advantage following such a situation, possibly stimulating recuperative behaviours (3). On the basis of this model it may be predicted that exposure to opioid-activating environmental stimuli would induce biphasic alterations in nociception with analgesia being evident in the first instance possibly followed by hyperalgesia. The following studies were designed in order to investigate this possibility further.

GENERAL METHOD

Animals

Twenty-five to 35 gram male DBA/2 mice (Bantin and Kingman, Hull, UK) were used. Animals were housed in groups of 10 (cage size $45 \times 28 \times 13$ cm) in a temperature-controlled room (24 ± 1°C) under 12-hr reversed light/dark cycle (lights off 0900 hr) with food and water available ad lib. Individually housed (cage size $33 \times 15 \times 13$ cm) male BKW (Bradford University Breeding Colony) maintained under the same housing conditions as above were also employed.

Apparatus

Nociception was measured using the tail-flick assay (Socrel Tail Flick Unit, Ugo Basile, Italy) with animals being hand-held and a single measure taken at each test point. Temperature was adjusted to give control latencies in the order of 3–4 sec using a cut-off of 8 seconds. These settings were chosen on the basis of pilot studies as being appropriate for the detection of both increases and decreases in pain sensitivity.

Social Encounters

DBA/2 mice were, in a standard resident-intruder paradigm, introduced into the home cage of a BKW. In instances where DBA/2s were attacked, the encounter was terminated upon the first unambiguous display of the upright submissive posture [as described in (6) and illustrated for the $B6AF_1/J$ strain in (13)] plus a further 35 bite attacks (attacked). These parameters were chosen as they had been previously shown to be the minimum criterion for the reliable induction of opioid-mediated analgesia (17,19). In instances where DBA/2 mice were not attacked these animals remained in the home cage of a BKW for a time equivalent to that required for attacked animals to reach criterion (nonattacked).

Drugs

Morphine sulphate and naloxone hydrochloride (Sigma, UK) were dissolved in 0.9% saline, which alone served as vehicle control. Injections were performed intraperitoneally in a volume of 10 ml/kg.

Procedure

All testing took place under dim red light during the midportion of the dark phase of the LD cycle. Prior to the start of experimentation animals were introduced into the laboratory environment and habituated for 1 hour. Following this period tail-flick latencies (TFL) were established for all animals (baseline or pre) except in the case of Experiment 4.

EXPERIMENT 1

For this study baseline TFLs were established, whereupon DBA/2 mice were placed into the home cage of a resident BKW which had been earlier screened to establish its aggressivity. On this basis, 10 DBA/2 were assigned to the nonattacked condition and 10 to the attacked. On no occasion was an attack observed on an animal in the nonattacked group. Following exposure to attack, or when time criteria had been reached, TFLs were established for all animals at 15, 45, 60, 75 and 90 minutes postencounter. TFLs were not established at 30 min in view of the evidence discussed above suggesting encounter-induced analgesias to have durations of <10 min or >45 min. Results from this study are presented in Fig. 1.

Two-factor Analysis of Variance (Factor A: attack condition, attacked or nonattacked: Factor B: time, pre, 15, 45, 60, 75 or 90 min postencounter) revealed significant effects of time, $F(5,90) = 9.17$, $p<0.01$, and a significant attack condition/time interaction, $F(5,90) = 5.67$, $p<0.01$. Follow-up orthogonal contrasts revealed these effects to be due to significant analgesia in the attacked condition (as compared to the nonattacked group) at 15 min postattack, $F(1,18) = 6.9$, $p<0.01$, and significant HYPERalgesia in these same animals at 75 min postattack, $F(1,18) = 4.51$, $p<0.05$. These data indicate that exposure to extended attack produces at least two distinct phases in nociceptive responding, early postattack analgesia followed by an hyperalgesic reaction some time after this form of environmentally-induced analgesia has dissipated.

EXPERIMENT 2

In view of the suggested involvement of endogenous opioids in the mediation of extended attack-induced analgesia (12,16), the following investigation was conducted to examine the possible role of opioid mechanisms in the mediation of extended attack-induced hyperalgesia.

For this investigation DBA/2 mice were exposed to the same attack parameters as described above. Following this procedure animals were assigned in randomised-counterbalanced order to receive either saline, 1 or 10 mg/kg naloxone with injections being given immediately or 1 hr postencounter and TFLs established 10 minutes after that. In all, there were six treatment combinations (saline, 1 or 10 mg/kg naloxone; TFL at 10 or 70 min postencounter; n = 8/gp). Results from this study are presented in Fig. 2.

Three-factor ANOVA (Factor A: postattack period, 10 or 70 min postencounter; Factor B: drug condition, saline, 1 or 10 mg/kg; Factor C: time, pre or postencounter, repeated measures on last factor) revealed significant effects of postattack period, $F(1,42) = 4.76$, $p<0.05$, drug condition, $F(2,42) = 3.32$, $p<0.05$, and a significant postattack period/drug condition interaction, $F(2,42) = 6.51$, $p<0.01$. There were further significant interactions between postattack period and time, $F(1,42) = 9.72$, $p<0.01$, drug condition and time, $F(2,42) = 4.24$, $p<0.025$, and a significant postattack period/drug condition/time interaction, $F(2,42) = 8.26$, $p<0.01$.

Further detailed analyses using Dunnett's t revealed these effects to be due to significant analgesia in saline-treated animals tested 10 min postencounter, $t(42) = 6.7$, $p<0.001$, and in mice given 1 mg/kg naloxone tested at the same time point, $t(42) = 3.39$, $p<0.01$. The absence of an analgesic reaction in animals treated with 10 mg/kg naloxone, $t(42) = 1.44$, ns, suggests that postencounter analgesia is blocked by pretreatment with this opiate antagonist.

Other effects were found to be due to significant hyperalgesia in saline-treated animals tail-flicked at 70 min postencounter, $t(42) = 3.41$, $p<0.01$, an effect not seen in mice administered with

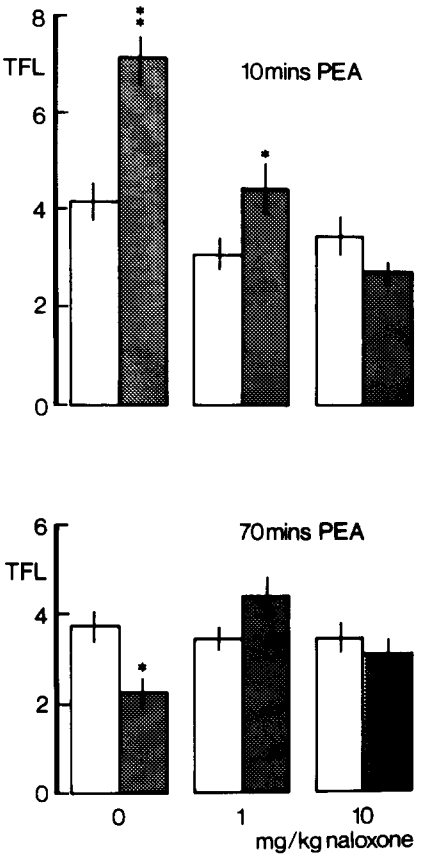

FIG. 2. Effects of naloxone on agonistic encounter-induced analgesia and hyperalgesia. Data are presented as mean TFLs. Open bars indicate baseline and filled bars represent postencounter measures. Analysis of these data indicated the analgesic response evident at 10 min postextended attack (PEA) to be reversed by 10 mg/kg naloxone, whilst the hyperalgesia observed at 70 min PEA was antagonised by 1 and 10 mg/kg. These data suggest these postencounter alterations in nociception to be mediated by substrates acting at opiate receptor mechanisms. See text for further details. $^{**}p<0.01$. $^{*}p<0.05$.

1, $t(42) = 2.3$, ns, or 10 mg/kg naloxone, $t(42) = 0.92$, ns, tested at the same time point. These data indicate the possible involvement of opioid mechanisms in the mediation of encounter-induced hyperalgesia.

EXPERIMENT 3

As several parallels exist between the actions of endogenous opioids and exogenous opiates, such as morphine, this study was performed to investigate whether hyperalgesia could be observed postopiate administration. Following the establishment of baseline TFLs, DBA/2 mice were randomly assigned in counterbalanced order to receive saline, 1, 5, 10 or 20 mg/kg morphine with TFLs again being assessed at 1, 2, 3, 4, 5 and 6 hr postinjection (n = 9/10/gp). Data from this study are summarized in Fig. 3.

Two-factor ANOVA (Factor A: drug condition, 0, 1, 5, 10 or 20 mg/kg morphine; Factor B: time, baseline, 1, 2, 3, 4, 5 or 6 hr postinjection, repeated measures on last factor) revealed significant effects of drug condition, $F(4,44) = 7.58$, $p<0.01$, significant effects of time, $F(6,264) = 33.05$, $p<0.01$, and a significant drug/time interaction, $F(24,264) = 8.34$, $p<0.01$. Further, more

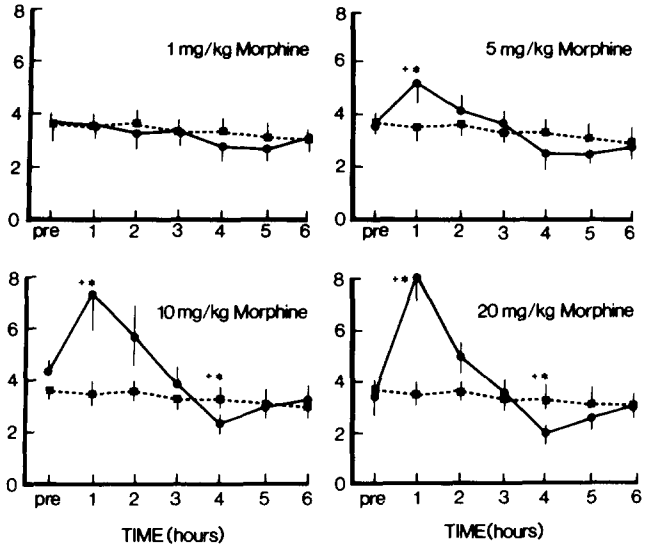

FIG. 3. Time course of alterations in nociception induced by morphine. Data are expressed as mean TFLs. The broken line represents saline-treated control values. Solid lines indicate TFLs of morphine-treated animals. One mg/kg morphine failed to significantly influence pain sensitivity. With 5 mg/kg morphine there was significant analgesia at 1 hr and a trend towards hyperalgesia between 4–5 hr postinjection. Ten and 20 mg/kg morphine both induced analgesia at 1 hr and significant hyperalgesia at 4 hr postadministration. These data indicate there to be at least two distinct phases in nociceptive responding following morphine injection and further suggest these effects to be dose-dependent. *$p<0.05$ from saline control at the same time point; +$p<0.05$ from baseline (pre) assessments.

detailed analyses using single factor ANOVA, orthogonal contrasts and Dunnett's t revealed these effects to be due to significant analgesia at 1 hr postinjection in 5, $F(1,44)=4.3$, $p<0.05$, 10, $F(1,44)=23.04$, $p<0.01$, and 20 mg/kg, $F(1,44)=33.69$, $p<0.01$, morphine-treated animals. Additional effects were found to be due to significant hyperalgesia at 4 hr postinjection in animals treated with 10, $t(44)=3.8$, $p<0.05$, 20 mg/kg, $t(44)=2.7$, $p<0.05$. Whilst animals treated with 5 mg/kg morphine did show a trend towards hyperalgesia at 4 hr postinjection, this did not reach significance, $t(44)=1.96$, ns. These data together, clearly demonstrate that morphine analgesia is followed by a period of hyperalgesia 4 hr postopiate injection and further suggest that this latter effect may be dose-dependent.

EXPERIMENT 4

In a manner directly analogous to Experiment 2, the following investigation was designed to examine the role of naloxone-sensitive opioid/opiate mechanisms in the mediation of morphine-induced hyperalgesia. For this study DBA/2 mice were assigned in randomised-counterbalanced order to receive saline, 5, 10 or 20 mg/kg morphine (MS). Following injection animals were left undisturbed for 3 hr 50 min and administered also in randomised counterbalanced order with saline, 1 or 10 mg/kg naloxone (NX). TFLs were established 10 min post final injection. In all, there were 12 treatment combinations (saline, 5, 10 or 20 mg/kg morphine followed by saline, 1 or 10 mg/kg naloxone n = 8/9/gp). Data from Experiment 4 are summarised in Fig. 4.

Two-factor ANOVA (Factor A: First treatment; saline, 5, 10 or 20 mg/kg morphine; Factor B: Second treatment; saline, 1 or 10 mg/kg naloxone) failed to reveal any effects of first treatment, $F(3,84)=1.003$, ns, second treatment, $F(2,84)=1.52$, ns, or any first treatment/second treatment interaction, $F(6,84)=1.82$, ns. However, in view of the experimental design involving antagonism studies, where a priori most groups may be expected not to differ from each other, follow-up tests were performed using orthogonal contrasts and Dunnett's t.

These more detailed analyses revealed significant effects amongst the saline second treatment group where those animals receiving 5, $t(84)=2.5$, $p<0.05$, 10, $t(84)=2.2$, $p<0.05$, or 20 mg/kg, $t(84)=2.9$, $p<0.05$, MS as first treatment all had significantly lower TFLs than those animals receiving saline as first treatment indicating the induction of hyperalgesia as a consequence of morphine administration. The naloxone sensitivity of this phenomenon is suggested by the lack of hyperalgesia as compared to saline/saline control, saline/NX 1 or saline/NX 10 mg/kg in any of the remaining morphine first treatment groups. However, the results are somewhat confounded by the trend towards hyperalgesia in the saline/NX 1 and saline/NX 10 mg/kg groups. Although these differences did not reach significance, $t(84)=1.67$, ns and $t(84)=1.37$, ns, respectively, these data question the utility of within treatments comparisons (i.e., saline/NX 1 mg/kg with MS 5 mg/kg/NX 1 mg/kg and MS 10 mg/kg/NX 1 mg/kg, etc.). Therefore, between treatments comparisons were used. These analyses revealed that the TFLs of mice treated with MS 5 or 10 mg/kg as first treatment and saline as second treatment did not differ significantly from those animals receiving MS 5 or 10 mg/kg followed by NX 1 or NX 10 mg/kg. Therefore, as these pain latencies did not differ it is difficult to interpret the lack of within groups effects in these treatment combinations as antagonism of morphine-induced hyperalgesia. However, the TFLs of animals receiving MS 20 mg/kg followed by 10 mg/kg NX were significantly greater than those in the MS 20/saline condition, $F(1,84)=5.14$, $p<0.05$, indicating that in this group at least, that this form of hyperalgesia is antagonised by opiate antagonists. These findings further indicate a relationship between the dose of morphine required to induce hyperalgesia and the amount of naloxone required to reverse this effect.

GENERAL DISCUSSION

Current data indicate that exposure to opioid activating environmental stimuli induces at least two distinct phases in subsequent responsivity to noxious stimulation. The early postexposure phase is characterised by analgesia whilst the later phase is associated with hyperalgesia. Both these phenomena are naloxone-reversible. These findings clearly indicate that alterations in nociceptive responding as a consequence of exposure to 'naturalistic' environmental stimuli depend upon not only the attack parameters employed, but temporal considerations also. Thus, the known sequence of events associated with exposure to an aggressive conspecific is 1) short-lasting (<10 min) nonopioid analgesia activated by residents' scent and moderate attack up to and including the first display of the upright submissive posture (17); 2) somewhat longer lasting (45–60 min) opioid-mediated analgesia induced as a consequence of exposure to encounters continuing beyond the first display of the upright submissive posture (12, 16, 17, 22), which may be associated with the ineffectiveness of the attacked animals social postures in reducing the severity of further attack or the "uncontrollability" of such stimuli (16); and 3) as indicated by present data, the onset of short-lasting hyperalgesia, mediated by naloxone-sensitive opioid-receptor systems, which is apparent in the late postattack period.

Interestingly, morphine administration appears to mimic the actions of endogenous opioids such that morphine-induced analgesia is also followed by a period of increased responsivity to noxious stimulation. It is, as yet, unclear as to whether analgesia

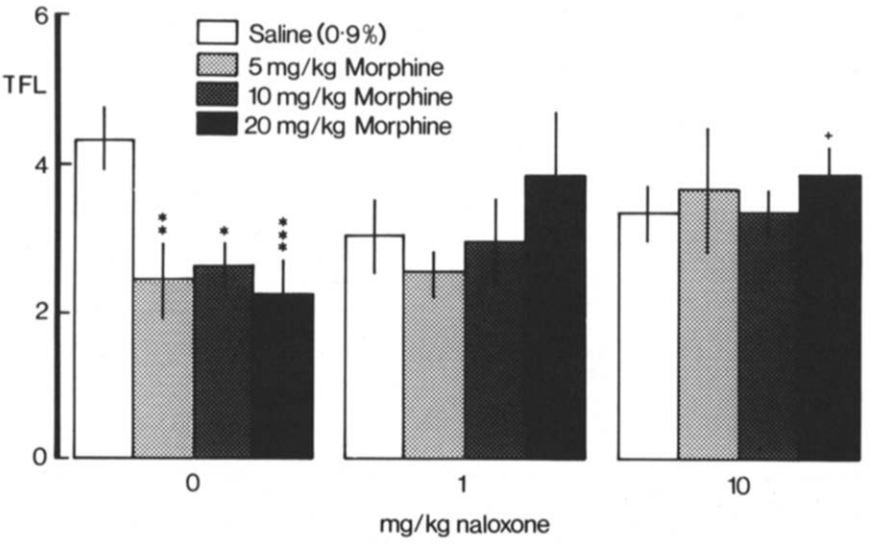

FIG. 4. Effects of naloxone on morphine-induced hyperalgesia. Data are presented as mean TFLs. Animals were treated with morphine (0–20 mg/kg) left undisturbed for 3 hr 50 min, injected with naloxone (0–10 mg/kg) and assayed for TFL at 4 hr postmorphine administration. Analysis revealed there to be significant hyperalgesia in DBA/2 mice treated with 5–20 mg/kg morphine followed by saline. These effects were apparently reversed by naloxone 1 and 10 mg/kg. However, between group comparisons revealed only the TFLs of animals treated with 20 mg/kg morphine followed by 10 mg/kg naloxone to be significantly greater than appropriate morphine/saline controls. Therefore, it is only in this former group that morphine-induced hyperalgesia may be viewed as being unequivocally reversed by naloxone. Nonetheless, these data do suggest morphine-induced hyperalgesia to be mediated by substrates acting at opiate receptors. They further suggest a relationship between the dose of morphine required to induce hyperalgesia and the amount of naloxone needed to reverse it. See text for further details. ***$p<0.001$; **$p<0.01$; *$p<0.05$; +$p<0.05$ from 20 mg/kg morphine/saline.

is an essential prerequisite for the onset of the hyperalgesia phase and current data do not allow firm conclusions to be drawn. However, animals treated with subanalgesic doses of morphine also fail to display hyperalgesia at 4 hr postinjection, whilst those treated with larger doses display both. The minimum effective dose of morphine for the expression of hyperalgesia under present experimental conditions appears to be within the order of 5–10 mg/kg as the lowest dose in this range produces significant analgesia yet only a trend towards hyperalgesia. These findings confirm and extend previous reports of hyperalgesia in rats up at 1–2 hr postmorphine administration (10). Further, in view of the ability of opiate antagonists to reverse this effect, current data allow the possibility that these forms of hyperalgesia are due to an effect of the absence of opioids/opiate per se to be dismissed. The naloxone reversibility of morphine-induced hyperalgesia under present circumstances is not as clear as in the case of environmentally-induced increases in nociception, as only hyperalgesia induced by the highest dose of morphine used was unequivocally antagonised by 10 mg/kg naloxone. Nonetheless, these data do suggest the involvement of opiate receptor mechanisms in the mediation of this response.

Doses of naloxone within the current range are usually held to be without significant intrinsic activity (20). However, where they have been found to induce alterations in nociception these have been in the direction of hyperalgesia, which has been viewed as being an artefact of the utilization of test situations which unintentionally activate endogenous opioid analgesia mechanisms (5). Therefore, it seems unlikely that the reversal of hyperalgesia by naloxone under present test conditions is due to an intrinsic effect of this antagonist per se, but rather that it is acting to attenuate the influence of an endogenous hyperalgesic ligand.

In this context, several groups have suggested the existence of an endogenous "opioid inverse agonist" (1, 2, 7) that is a ligand that, whilst acting upon opiate receptor mechanisms, induces functional consequences opposite to those normally ascribed to traditional opiate agonists. More specifically, adrenocorticotropin (ACTH) has been considered to be a prime candidate for this role in view of its close association with β-endorphin in terms of biosynthesis, distribution (15), their mutually antagonistic interactions (1, 2, 21) and the ability of naloxone to reverse many ACTH-induced effects (2, 4, 9).

Whilst these findings are suggestive of a role for ACTH in the mediation of hyperalgesia observed under present circumstances, a number of other observations are at variance with this hypothesis. For example, dexamethasone is without effect on the development of attack-induced analgesia and corticosterone administration or adrenalectomy actually enhance this reaction (13). Further, mice exposed to extended attack show increased levels of plasma corticosterone in conjunction with analgesia [although there is no significant correlation between these effects, (13)]. Together, these data indicate that the activation of the pituitary-adrenal axis is not related to the expression of attack-induced analgesia. However, in view of the existence of both central and peripheral POMC systems (15), and given that opioids and/or opiates stimulate ACTH release (9, 10, 12, 22), it has been suggested that the measurement of CNS *and* plasma opioid/ACTH *ratios* may be a more accurate reflection of the interaction between these peptides than measurements of plasma opioid or ACTH levels per se (7). Nonetheless, in the absence of further data, any suggested role for ACTH as an endogenous opioid inverse agonist must remain highly speculative.

In summary, present findings indicate that both opioid and

opiate analgesia are followed by short-lasting hyperalgesia. The naloxone-reversibility of these phenomena strongly indicate that these responses reflect the actions of an endogenous opioid inverse agonist. Current data do not allow firm conclusions to be drawn as to the identity of this ligand, however, evidence does suggest that ACTH has many of the properties that an opioid inverse agonist would be expected to possess, in terms of biosynthesis, distribution, receptor affinity, interactions with opioids/opiates and its effects per se. Studies are currently underway in this laboratory to investigate this and the hypothesis of Bolles and Fanselow (3) suggesting that encounter-induced hyperalgesia may be correlated with the expression of recuperative behaviours.

REFERENCES

1. Amir, S. Effects of ACTH on pain responsiveness in mice: Interaction with morphine. Neuropharmacology 20:959–962; 1981.
2. Bertolini, A.; Poggioli, R.; Fratta, W. ACTH-induced hyperalgesia in rats. Experientia 35:1216–1217; 1978.
3. Bolles, R. C.; Fanselow, M. S. A perceptual-defensive-recuperative model of fear and pain. Behav. Brain Sci. 3:291–323; 1980.
4. Gispen, W. H.; Wiegant, W. M. Opiate antagonists suppress ACTH-induced excessive grooming in the rat. Neurosci. Lett. 2:159–164; 1976.
5. Goldstein, A. Endorphins and pain: A critical review. In: Beers, R. F.; Bassett, E. G., eds. Mechanisms of pain and analgesic compounds. New York: Raven Press; 1979:249–262.
6. Grant, E. C.; MacKintosh, J. H. A comparison of the social postures of some common laboratory rodents. Behaviour 21:246–259; 1963.
7. Hendrie, C. A. Opiate dependence and withdrawal: A new synthesis? Pharmacol. Biochem. Behav. 23:863–870; 1985.
8. Jezova, D.; Vigas, M.; Jurcovicova, S. ACTH and corticosterone response to naloxone in normal and hypophysectomized and dexamethasone treated rats. Life Sci. 31:307–314; 1982.
9. Jolles, J.; Wiegant, W. M.; Gispen, W. H. Reduced behavioural effectiveness of ACTH after a second administration: Interactions with opiates. Neurosci. Lett. 9:261–266; 1978.
10. Kayan, S.; Woods, L. A.; Mitchell, C. L. Morphine-induced hyperalgesia in rats tested on the hot-plate. J. Pharmacol. Exp. Ther. 177:509–513; 1971.
11. Lotti, V. S.; Kokka, N.; George, R. Pituitary-adrenal activation following intrahypothalamic microinjection of morphine. Neuroendocrinology 4:326–332; 1969.
12. Miczek, K. A.; Thompson, M. L.; Shuster, L. Opioid-like analgesia in defeated mice. Science 215:1520–1522; 1982.
13. Miczek, K. A.; Thompson, M. L.; Shuster, L. Analgesia following defeat in an aggressive encounter: Development of tolerance and changes in opioid receptors. Ann. NY Acad. Sci. 467:14–29; 1986.
14. Morley, J. E. Synthetic endorphins. In: Eberie, A.; Geiger, R.; Wiezand, J., eds. Perspectives in peptide research. Basel: J. Karger; 1981:329–343.
15. O'Donohue, T. L.; Dorsa, D. M. The opiomelanotropinergic neuronal and endocrine systems. Peptides 3:353–395; 1982.
16. Rodgers, R. J.; Hendrie, C. A. Social conflict activates status-dependent endogenous analgesic or hyperalgesic mechanisms in male mice: Effects of naloxone on nociception and behaviour. Physiol. Behav. 30:775–780; 1983.
17. Rodgers, R. J.; Randall, J. I. Social conflict analgesia: Studies on naloxone antagonism and morphine cross-tolerance in male DBA/2 mice. Pharmacol. Biochem. Behav. 23:883–888; 1985.
18. Rodgers, R. J.; Randall, J. I. Acute non-opioid analgesia in defeated male mice. Physiol. Behav. 36:947–950; 1986.
19. Rodgers, R. J.; Randall, J. I. Social conflict analgesia: Inhibition of early non-opioid component by diazepam or flumazepil fails to affect appearance of late opioid component. Brain Res. Bull. 19:141–144; 1987.
20. Sawynok, J.; Pinsky, C.; Labella, F. S. On the specificity of naloxone as an opiate antagonist. Life Sci. 25:1621–1632; 1979.
21. Terenius, L. Somatostatin and ACTH are peptides with partial antagonist-like selectivity for opiate receptors. Eur. J. Pharmacol. 38:211–213; 1976.
22. Teskey, G. C.; Kavaliers, M.; Hirst, M. Social conflict activates opioid analgesic and ingestive behaviours in mice. Life Sci. 35: 303–315; 1984.
23. Van Vugt, D. A.; Meites, J. Influence of endogenous opiates on anterior pituitary function. Fed. Proc. 39:2533–2538; 1980.
24. Watkins, L. R.; Mayer, D. J. Organisation of endogenous opiate and non-opiate pain control systems. Science 216:1185–1192; 1982.
25. Watkins, L. R.; Mayer, D. J. Multiple endogenous opiate and non-opiate analgesia systems: Evidence for their existence and clinical implications. Ann. NY Acad. Sci. 467:274–299; 1986.