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ENHANCEMENT OF MORPHINE ANALGESIA IN RATS FOLLOWING REMOVAL FROM CONTEXTUAL CONDITIONED FEAR CUES

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Abstract

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1. Previous studies have shown that morphine analgesia is enhanced when analgesia testing is conducted in an environment that has been previously paired with shock, but not in a novel or neutral environment.
2. Two experiments were conducted to assess if enhanced morphine analgesia could be demonstrated in a neutral context if rats were first exposed to conditioned fear cues. This was done by pre-exposing rats to a context previously paired with shock and testing for enhanced morphine analgesia in a neutral context immediately following removal from the conditioned fear context. To determined if conditioned analgesia contributed to the enhanced morphine analgesia, rats were tested for analgesic responsiveness immediately following removal from conditioned fear cues, prior to morphine administration.
3. In Experiment 1, although conditioned analgesia was not observed, a small enhancement of morphine analgesia was demonstrated in an neutral context in rats pre-exposed to conditioned fear cues, compared to non-conditioned controls.
4. In Experiment 2, which employed more sensitive test procedures, a strong enhancement of morphine analgesia was observed in a neutral context only in those rats that demonstrated conditioned analgesia.

Keywords: fear conditioning, individual differences, inescapable foot shock, opioids, stress, tail-flick.

Abbreviations: conditioned fear (CF), conditioned fear-analgesia (CF-A), conditioned fear-no analgesia (CF-NA), foot shock (FS), no conditioned fear (NCF).

Introduction

It is well established that physical stressors such as restraint (Appelbaum and Holtzman, 1985; Appelbaum and Holtzman, 1984; Calcagnetti et al., 1990; Calcagnetti and Holtzman, 1992; Calcagnetti and Holtzman, 1990; Fleetwood and Holtzman, 1989), forced swim (Baamonde, et al., 1989), electroconvulsive shock (Belenky and Holaday, 1981) inescapable tail shock (Grau et al., 1981; Hyson et al., 1982; Maier, 1986), and inescapable foot shock (Lewis et al., 1981) enhance the analgesic effects of opiates. Exposure to the environmental stimuli present during administration of a physical stressor can also affect opiate reactivity. For example, the analgesic effects of morphine are enhanced when analgesia testing is conducted in an environment previously paired with shock (the conditioned fear context) (Abrahamsen et al., 1993; Przewlocka et al., 1990; Rosellini et al., 1994; Sherman et al., 1984). Although enhancement of morphine analgesia has been demonstrated in the presence of conditioned fear cues, studies have failed to observe the enhancement in previously shocked subjects if analgesia testing was conducted in the absence of conditioned fear cues. For example, Sherman et al. (1984) showed that rats shocked and tested in the conditioned fear context displayed enhanced morphine analgesia, but rats shocked in the home cage and tested in a different environment did not display the enhancement. Similarly, Abrahamsen et al. (1993) found that foot shock enhanced morphine analgesia when testing was conducted in the conditioned fear context, but not when testing was carried out in a novel context.

Exposure to a conditioned fear context has been shown to elicit a pronounced conditioned analgesic response in the absence of morphine administration (Fanselow, 1984; MacLennan et al., 1980; Maier, 1989; Sherman et al., 1984; Watkins et al., 1982). Evidence suggests that conditioned analgesia may contribute to the enhancement of morphine analgesia. Enhanced morphine analgesia has been demonstrated under conditions that not only produce conditioned fear (Rosellini et al., 1994) but also under conditions that elicit conditioned analgesia (Sherman et al., 1984; Przewlocka et al., 1990). Because conditioned analgesia has been shown to be mediated by endogenous opioids (Abrahamsen et al., 1995; Fanselow, 1984; Fanselow and Baackes, 1982; Lichtman and Fanselow, 1991; Sherman et al., 1984), it has been suggested that enhanced morphine analgesia results from an additive combination of opioid-mediated analgesia produced by context conditioned fear with morphine-induced analgesia (Abrahamsen et al., 1993; Sherman et al., 1984). Although enhanced

morphine analgesia and conditioned analgesia have often been shown to occur in conjunction, this phenomenon has not always been demonstrated (Abrahamsen et al., 1993; Sherman et al., 1984).

The purpose of the present studies was to determine if conditioned analgesia is necessary for enhanced morphine analgesia to occur. This was done by testing for conditioned analgesia in a neutral context immediately following the removal of contextual conditioned fear cues. Immediately following conditioned analgesia testing, rats were administered morphine and tested for enhanced morphine analgesia in a neutral context.

Experiment 1

Methods

Animals. Seventeen experimentally naive adult male Sprague Dawley rats (Harlan, Altamont, NY), ranging in weight from 280-340 g, were used in this study. Rats were housed under a 12 hr light/dark cycle, with the light onset at 7 am, and were provided with *ad libitum* Purina Rat Chow and water throughout the study. All procedures used in these studies were approved by the University Animal Welfare Committee.

Drugs. Morphine sulfate (Sigma Chemical Co., St. Louis, MO) was dissolved in 0.9% saline solution at a concentration of 1.0 mg/ml. Injections were administered subcutaneously (sc) at a dose of 1.0 mg/kg.

Apparatus. Four chambers were used to administer shock. Each measured 21.0 x 30.5 x 27.9. The walls were constructed of aluminum and the ceiling and door of clear Plexiglas. The floor consisted of stainless steel rods of 3.0 mm in diameter and spaced 1.2 cm apart. A 28 V DC houselight was located 29 cm above the grid floor and was centered on the front wall. Scrambled shock (0.9 mA) was delivered to the grid floor of the chambers by solid-state shock sources (Coulbourn Instruments Model 13-16). These chambers were housed in boxes equipped with ventilating fans that also provided background masking noise.

Four different chambers, each measuring 30 x 30 x 30 cm, were used as the neutral context. The walls were constructed of aluminum, the ceiling and door of clear Plexiglas, and the floor of wire mesh. Lights and ventilating fans

were not present in these chambers, which were located in a separate room from the shock context chambers.

Analgesia testing was conducted using a tail-flick apparatus, which is described in detail in Abrahamsen et al. (1993). The light intensity of the lamp was regulated by a variable autotransformer set at 85 V-AC, which produced a baseline tail-flick latency between 3-4 sec.

Procedure

Habituation. Rats were habituated to handling, the tail-flick apparatus, and the injection procedure for two days prior to the beginning of the experiment. Habituation to the tail-flick apparatus involved gently wrapping the rat in a towel and manually restraining it on the apparatus for several seconds. On Days 1 and 2, rats were exposed to the neutral context chambers for 30 min.

Fear Conditioning. On Days 3 and 4, one group of rats received contextual fear conditioning (Group Conditioned Fear (CF), n=9), consisting of one 30 min session each day of 20 trials of 5 sec 0.9 mA shock. Similar parameters previously have been shown to condition high levels of fear to a context (Rosellini et al., 1994; Rosellini et al., 1987). A second group received no contextual fear conditioning (Group No Conditioned Fear (NCF), n=8). This group received 30 min of exposure to the chamber, but was not shocked. Different experimenters were used for the fear conditioning and analgesia testing phases to minimize the possibility of generalization of fear to the experimenter.

Analgesia Testing. On Day 5, approximately 24 hrs after the last conditioning session, rats were gently wrapped in a towel and were manually restrained on the tail-flick apparatus. The rat's tail was exposed from the towel and was positioned directly above the light source. Upon receipt of radiant heat from the light, a tail-flick was scored as a lateral deflection of the tail such that the tail no longer covered the light source. Special care was taken to ensure that a rat did not receive repeated tests on the same portion of the tail. Two baseline tail-flick tests, separated by a 1-min interval, were administered in the colony room. A 10 sec cutoff latency was used to prevent tail damage. These two tests were averaged to yield a baseline score. After baseline testing, rats were placed into the conditioning chambers for 15 min and immediately thereafter transported to the

neutral context. Prior to being placed into the neutral context chambers, one immediate tail-flick test was given to assess if any residual conditioned analgesia was present after removal from context conditioned fear cues. Subsequently, rats were given a 1.0 mg/kg sc injection of morphine and placed into the neutral context chamber. One tail-flick test was administered at 5, 10, 20, 30, 45, and 60 min following morphine injection.

Data Analysis

All data analyses were conducted using repeated measures analysis of variance (ANOVA). Newman-Keuls post hoc tests ($p < .05$) were used to assess the source of significant effects.

Results

Assessment of Residual Conditioned Analgesia

Panel A of Fig 1 illustrates that rats which were exposed to the conditioned fear context before analgesia testing (Group CF) and rats that received no fear conditioning (Group NCF) did not differ in baseline tail-flick latencies. CF and NCF rats also did not differ in tail-flick latencies when tested in a neutral environment following removal from the conditioning context, prior to morphine administration (immediate test). These observations were confirmed by a repeated measures ANOVA conducted on the baseline and immediate tests. No significant group differences between CF and NCF rats were found on these tests.

Assessment of Enhanced Morphine Analgesia

Panel B of Fig 1 illustrates tail-flick latencies following morphine administration. A repeated measures ANOVA conducted on the time points following morphine administration revealed a significant main effect of Group (CF vs. NCF) ($F(1,15) = 5.70$, $p = .031$) and Test (5, 10, 20, 30, 45, and 60 min) ($F(5,75) = 4.23$, $p = .002$), but no significant Group X Test interaction. However, post-hoc tests comparing the group means collapsed over the six tests as well as at each separate time point failed to reach significance.

Experiment 2

The first purpose of Experiment 2 was to replicate the enhanced morphine analgesia observed in Experiment 1. Because of the small increase in morphine

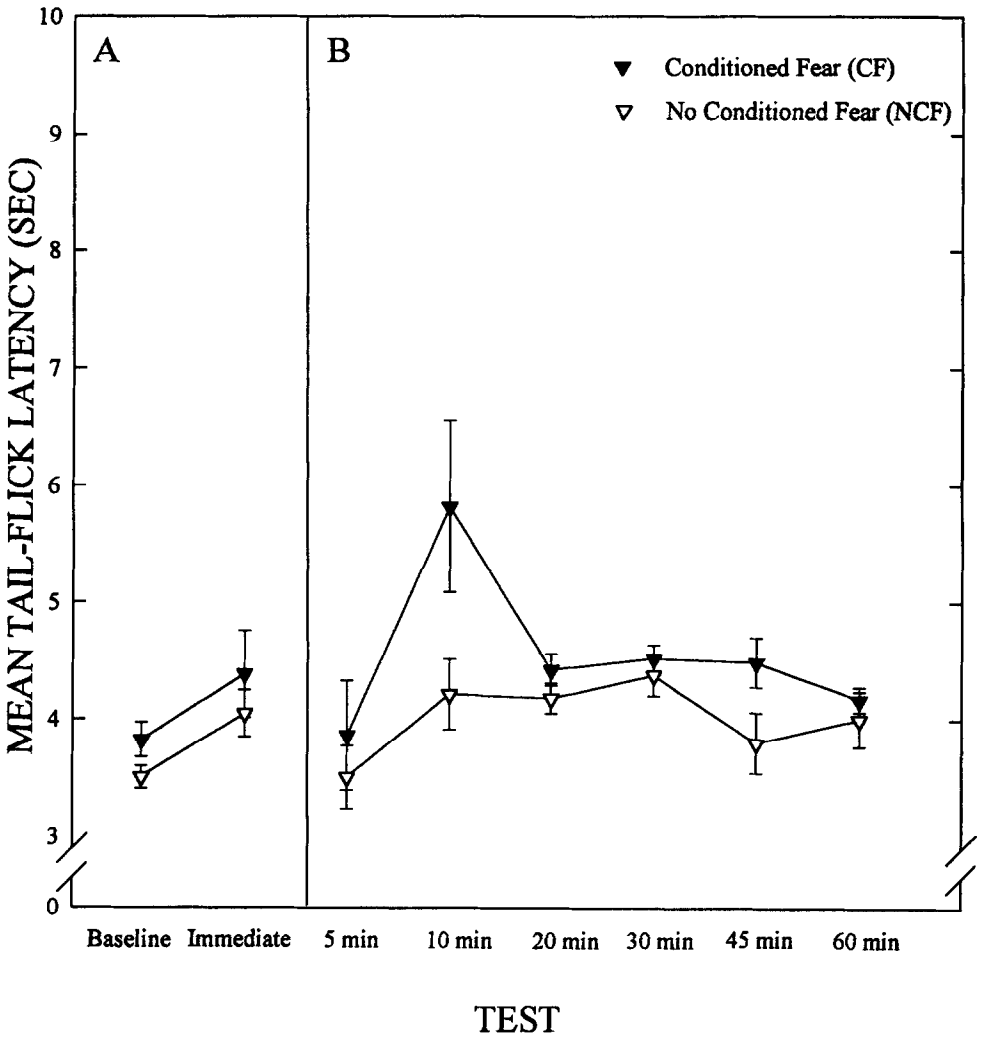

Fig 1. Panel A shows the mean (±S.E.) tail-flick latencies prior to (Baseline) and immediately following (Immediate) removal from the conditioned fear context (CF, n=9) or a context not associated with shock (NCF, n=8). Panel B shows the mean (±S.E.) tail-flick latency following morphine administration (1 mg/kg) in a neutral context.

analgesia in CF rats in Experiment 1, two additional modifications were made to control for and reduce the chances of observing direct shock effects on morphine analgesia. First, a control group was added that received shock but was not exposed to conditioned fear cues on the test day. Second, testing was conducted 72 instead of 24 hours after shock exposure, because shock-induced enhancement of morphine analgesia has been reported to dissipate by 48 hrs (cited in Sherman et al., 1984). The second purpose Experiment 2 was to attempt to observe conditioned analgesia by using more sensitive testing procedures. The light intensity of the tail-flick apparatus was lowered in Experiment 2, because studies have shown that previously subthreshold conditioned analgesia can be detected by lowering the stimulus intensity of a hot plate (Sherman et al., 1984).

Methods

Animals, Drug, and Apparatus. Thirty-six experimentally naive male Sprague-Dawley rats, ranging in weight from 290-370 g, were used in this study. The shock, neutral context chambers, and tail-flick apparatus were identical to those used in Experiment 1. Drugs, dosage, and administration were identical to that described in Experiment 1. A second distinct neutral context, measuring 57 x 28 x 20 cm, was also utilized in this experiment. The front wall was clear Plexiglas, the left side horizontal black and white stripes, the right side uniform gray, and the floor consisted of wire mesh.

Procedure. Rats were habituated to handling, the tail-flick apparatus, and the injection procedure in a manner identical to Experiment 1. On Days 1 and 2, rats were exposed to both the first neutral context (as in Experiment 1) and the second neutral context chambers for 30 minutes.

This study replicated the design of Experiment 1 utilizing both CF (n=12) and NCF (n=12) groups. However, several important modifications were made. First, a foot shock (FS, n=12) control group was utilized that received the same amount of shock exposure as CF rats. On the day of testing, however, FS rats were not exposed to the conditioned fear context but instead were exposed to the second neutral context chambers for 15 minutes prior to analgesia testing. Second, rats were tested 72, instead of 24 hrs after the second day

of contextual fear conditioning. Third, the light intensity of the apparatus was lowered to 70 V-AC, and the cutoff latency was increased to 15 seconds. This light intensity produced baseline latencies of about 5 sec. Based on pilot data, it was anticipated that under the conditions of the present experiment some rats would exhibit analgesia on the immediate test. Because these pilot data suggested that individual differences may be important in the conditioned analgesia measure, breakdowns were utilized similar to those employed by others (Drugan et al., 1993). In the present study, rats were separated on the basis of the analgesia response on the immediate tail-flick test. Rats were considered analgesic if they demonstrated a 50% or greater increase in latency on the immediate tail-flick test above the mean of the baseline tests.

Results

Assessment of Residual Conditioned Analgesia: Separation into Groups of Responders and Non-Responders

Analgesia on the immediate test was observed in 4 of 12 rats in the CF group. No rats in either the NCF or FS groups exhibited analgesia on the immediate test. Furthermore, in CF rats that exhibited analgesia on the immediate test, significant positive correlations were observed between the tail-flick latencies on the immediate tests and the 5 min, 10 min, 20 min, and 30 min tests (.82, $p < .01$; .69, $p < .05$; .87, $p < .01$; .70, $p < .05$ respectively), but not the 45 and 60 min tests. No significant positive correlations were observed between the immediate test and the tests following morphine administration for NCF and FS groups. Based on these results, CF rats were divided into two groups for further analyses: those showing analgesia (CF-A, n=4) and those showing no analgesia (CF-NA, n=8) on the immediate test. These correlations indicated that only rats which exhibited analgesia on the immediate test also demonstrated enhanced morphine analgesia.

Panel A of Fig 2 illustrates that rats which were exposed to conditioned fear cues before analgesia testing either exhibited a pronounced analgesia (Group CF-A) or showed no analgesia (Groups CF-NA) on the immediate test. Rats that received no context fear conditioning (Group NCF) and rats that received foot shock and were exposed to a neutral context before analgesia testing (Group FS) did not demonstrate analgesia on the immediate test. No group differences were observed on the baseline test. These observations were

confirmed by a repeated measures ANOVA conducted on the baseline and immediate tests. A significant Group (CF-A, CF-NA, NCF, FS) x Test (baseline and immediate) interaction was found for these tests ($F(3,32) = 48.73$, $p < .001$). Post hoc tests confirmed that although the groups did not differ on the baseline test, CF-A had longer latencies on the immediate test ($p < .05$) than all other groups, which did not differ from each other.

Assessment of Enhanced Morphine Analgesia

Panel B of Fig 2 illustrates that all groups exhibited increasing tail-flick latencies following morphine administration and that all groups appeared to show a maximum response at 20 min following morphine administration. CF-A rats, however, showed the greatest enhancement of morphine analgesia. A repeated measures ANOVA on the tests following morphine administration revealed a significant Group x Test (5, 10, 20, 30, 45, and 60 min) interaction, $F(5, 15) = 3.01$, $p < .001$). Post hoc tests confirmed that CF-A rats had significantly longer tail-flick latencies on the 5, 10, 20, and 30 min tests as compared to all other groups. Furthermore, significant main effects of both Group ($F(3,32) = 8.27$, $p < .001$) and Test ($5,160) = 8.97$, $p < .001$) were found, suggesting that although morphine elevated tail-flick latencies for all groups, CF-A rats showed the greatest enhancement.

These results demonstrated that only rats that exhibited analgesia on the immediate test also showed enhanced analgesia following morphine administration (Group CF-A). This suggests that analgesia resulting from exposure to conditioned fear cues must occur to observe enhanced morphine analgesia.

Discussion

The purpose of the present experiments was to assess the mechanism by which contextual conditioned fear can enhance morphine analgesia. This was accomplished by testing if enhanced morphine analgesia could be observed in a neutral context immediately following removal of conditioned fear cues and assessing whether conditioned analgesia contributed to any observed enhancement.

Enhanced Morphine Analgesia Following Removal of Conditioned Fear Cues

Experiment 1 revealed a small enhancement of morphine analgesia, but no evidence of conditioned analgesia, in rats following removal from conditioned

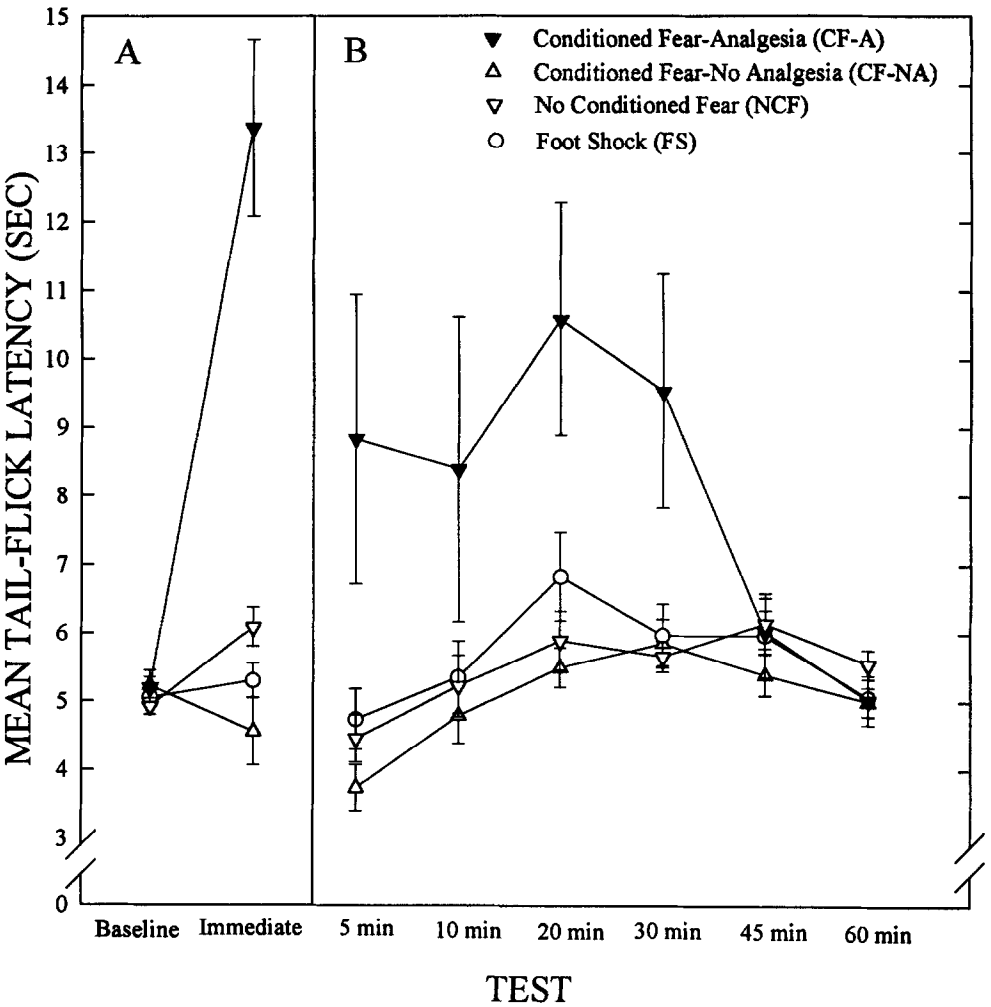

Fig 2. Panel A shows the mean (±S.E.) tail-flick latencies prior to (Baseline) and immediately following (Immediate) removal from the conditioned fear context (CF-A [n=4], CF-NA [n=8]) or a context not associated with shock (NCF [n=12], FS [n=12]). Rats that received context fear conditioning and were exposed to fear cues prior to analgesia testing either exhibited conditioned analgesia (CF-A) or showed no conditioned analgesia (CF-NA) on the immediate tail-flick test. NCF rats did not receive context fear conditioning and FS received foot shock but were not exposed to fear cues prior to testing. Panel B shows the mean (±S.E.) tail-flick latency following morphine administration (1 mg/kg) in a neutral context.

fear cues compared to non-conditioned controls. Because direct effects of shock could have accounted for this small increase, a second experiment was conducted that utilized additional control groups and more sensitive testing procedures. Experiment 2 demonstrated that enhanced morphine analgesia could be demonstrated following removal from the conditioned fear context. In this study, however, only rats that were exposed to context conditioned fear cues and exhibited an elevated analgesia upon removal from these cues showed the enhanced morphine analgesia. This suggests that analgesia resulting from the exposure to conditioned fear cues may have contributed to the enhanced morphine analgesia in these rats.

In Experiment 2, the exhibition of analgesia in following removal from contextual conditioned fear cues represents a novel finding. It has previously been reported that analgesia diminishes to undetectable levels following removal of conditioned fear cues (Maier, 1989). Initial examination of the results of Experiment 2 appeared to support this finding, because when the data were examined collapsed across CF-A and CF-NA groups no analgesia was apparent. Further examination of the data from Experiment 2, however, revealed a pronounced analgesia in a subset (4/12; 33%) of these rats (Group CF-A). It is possible that the analgesia following removal from conditioned fear cues has not previously been reported because the analgesia was evident statistically only after rats were divided into CF-A and CF-NA groups.

It is unlikely that a general shock-induced sensitization of the opioid system could account for the enhanced analgesia observed in Experiment 2. In this experiment several modifications were made to assess and control for the possibility that shock-induced sensitization could account for the enhanced morphine analgesia. First, a control group was added that received equivalent shock exposure as CF rats, but was not exposed to contextual fear cues before analgesia testing (Group FS). Second, a 72 hour interval was interposed between shock and analgesia testing. Conditioned fear effects are known to be temporally robust (Abrahamsen et al., 1995; Hendersen, 1978; Hoffman et al., 1963; Macintosh, 1974) whereas shock-induced stress effects such as sensitized neophobia (Minor, 1990) and sensitized fear systems (Maier, 1990) diminish within a 72 hour period. In Experiment 2, FS rats showed no evidence of enhanced morphine analgesia suggesting that, under these conditions, foot shock by itself did not induce a behavioral sensitization of morphine

analgesia. Instead it appears that exposure to conditioned fear cues prior to morphine administration enhanced analgesia in a subset of rats that displayed analgesia immediately following removal from conditioned fear cues.

Conditioned Analgesia Contributes to Enhanced Morphine Analgesia

The enhanced morphine analgesia observed in Experiment 2 most likely resulted from an interaction between morphine and a residual conditioned analgesia. It is unlikely that residual conditioned analgesia, in the absence of morphine, could produce a sustained analgesia up to 45 minutes after removal from conditioned fear cues. Using identical shock parameters, the authors have demonstrated that conditioned analgesia peaks 15-20 minutes after exposure to the conditioned fear context and is no longer detectable at 30 minutes, when rats are tested in the presence of conditioned fear cues (Abrahamsen et al., 1995; unpublished data). In Experiment 2, a significant enhancement of morphine analgesia was observed 30 minutes after morphine administration (more than 45 minutes after initial exposure to conditioned fear cues). Given that we observed no evidence of conditioned analgesia or freezing 30 minutes after exposure to conditioned fear cues when rats were tested in the conditioned fear context (unpublished data), it is unlikely that analgesia resulting from exposure to conditioned fear cues in the absence of morphine would be detectable 30 minutes following removal from the conditioned fear context.

Influence of Endogenous Opioids on Enhanced Morphine Analgesia

It is not known whether the analgesia on the immediate test following removal from conditioned fear cues in Experiment 2 is mediated by the endogenous opioid system. However, existing research would suggest that the analgesia on the immediate test in CF-A rats is in fact opioid mediated (Fanselow, 1984; Fanselow and Baackes, 1982; Sherman et al., 1984). Previous work from our laboratory has demonstrated that the shock parameters used in the present study produced a naloxone reversible conditioned analgesia when rats were tested in the conditioned fear context (Abrahamsen et al., 1995). Therefore, it is possible that in the present experiment, opioid mediated analgesia produced by context conditioned fear was still present when rats were tested for analgesia on the immediate test. If conditioned fear activated endogenous opioid activity and elevated analgesia on the immediate test in CF-A rats, the endogenous opioid system may have influenced the enhanced morphine

analgesia on the 5, 10, 20, and 30 min tests. To determine this issue, further studies examining if naloxone can block the analgesia following removal from context conditioned fear cues must be conducted.

Conclusion

Contextual conditioned fear can enhance morphine analgesia in a neutral context immediately following removal from the conditioned fear context. However, a marked enhancement of morphine analgesia was observed only in individuals that demonstrated a residual conditioned analgesia. This suggests that conditioned fear may enhance morphine analgesia through a mechanism involving the additive effects of endogenous opioids (produced by conditioned analgesia) and exogenous morphine. These findings also emphasize the importance of examining individual differences when studying the effects of stress on drug reactivity.

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