Brief Communication

Frontal Cortex Lesions Block the Opioid and Nonopioid Hypoalgesia Elicited by Brief Shocks but Not the Nonopioid Hypoalgesia Elicited by Long Shocks

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Previous research (Grau, 1987a, 1987b) suggests that forebrain systems play an essential role in the hypoalgesia observed after brief shock but not long shock. Additional research has shown that pentobarbital anesthesia and decerebration block the hypoalgesia observed after 3 brief (0.75-s) shocks but not the hypoalgesia observed after 3 long (25-s) shocks. This is a study of whether a specific forebrain lesion, a frontal cortex lesion, would have a similar impact on hypoalgesia induced by brief (0.75-s) and long (25-s) shocks. Frontal cortex lesions, like decerebration and pentobarbital anesthesia, eliminated the hypoalgesia observed after brief but not long shocks. Because other research suggests that the stress of surgery may influence whether the hypoalgesia elicited by shock is opioid or nonopioid, the 2nd experiment was to examine whether the sham operation per se alters the form of the hypoalgesia observed after brief shock. It does not; in the sham-treated subjects, brief shock induced the usual transient nonopioid hypoalgesia followed by prolonged opioid hypoalgesia. These data suggest that frontal cortex lesions block nonopioid and opioid hypoalgesia observed after brief shock.

Considerable evidence suggests that exposure to aversive environmental stimuli, such as electric shock, cold water, or biting, can suppress pain reactivity in animals (Akil, Madden, Patrick, & Barchas, 1976; Bodnar, Kelly, Brutus, & Glusman, 1980; Miczek, Thompson, & Shuster, 1982), including humans (Willer & Abel-Fessard, 1980; Willer, Dehen, & Cambier, 1981). This decrease in pain reactivity, or hypoalgesia, is thought to be mediated by a descending pain-control pathway that originates in the brainstem and inhibits the transmission of nociceptive information within the spinal cord dorsal horn (for a review, see Basbaum & Fields, 1984). In many situations, hypoalgesia appears to be mediated by an endogenous opioid system because the hypoalgesia can be blocked by opiate antagonists (e.g., naltrexone or naloxone) and morphine tolerance (Akil et al., 1976; Drugan, Grau, Maier, Madden, & Barchas, 1981; Fanselow & Barches, 1982; Grau, Hyson, Maier, Madden, & Barchas, 1981; Lewis, Cannon, & Liebeskind, 1980; Terman, Shavit, Lewis, Cannon, & Liebeskind, 1984; Watkins & Mayer, 1982). However, under other conditions, hypoalgesia appears to be “nonopioid” because it is not affected by these manipulations (Fanselow, 1984; Grau et al., 1981; Lewis et al., 1980; Lewis, Sherman, & Liebeskind, 1982; Watkins & Mayer, 1982).

There are two ways by which hypoalgesic systems might be activated. One possibility is that they are activated directly, at the level of the brainstem, by incoming nociceptive information (Terman et al., 1984). Alternatively, forebrain systems may, through descending fibers, control the activation of the hypoalgesic systems. We have suggested (Grau, 1987a, 1987b; Meagher, Grau, & King, in press) that the direct mode of activation may be used only when an organism experiences severely aversive stimuli and that forebrain systems normally mediate the activation of the hypoalgesic systems when an organism is exposed to mildly aversive events. Supporting this hypothesis, we have shown (Grau, 1987a; Grau & Meagher, 1988; Meagher et al., in press) that manipulations designed to disrupt forebrain systems, decerebration and administration of a high dose of pentobarbital, block the hypoalgesia observed after mild shock, but not severe shock, with shock severity being defined in terms of shock duration (mild, three “brief” [0.75-s] 1-mA shocks; severe, three “long” [25-s] 1-mA shocks). However, pentobarbital anesthesia and decerebration do much more than simply disrupt forebrain systems; they also disrupt various other systems (e.g., blood pressure, sympathetic function, and activation of the pituitary-adrenal axis; Richards, 1978; Woods, 1964) that often play an important role in environmentally induced hypoalgesia. For these reasons, in this study, we explored the impact of a manipulation that should have a much more selective impact on forebrain function: a lesion of the frontal cortex.

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General Method

Subjects

The subjects were male Sprague-Dawley rats obtained from Charles River Laboratories. The rats were 100–120 days old and weighed 420–540 g. Animals were housed individually and maintained on ad-libitum food and water. Sixty rats were used in Experiment 1, and 32 rats were used in Experiment 2.

Surgery and Histology

Rats were anesthetized with 40 mg/kg thiopental sodium, a short-acting anesthetic. After leveling the head with the aid of a stereotaxic instrument, an anterior–posterior incision was made in the scalp. A square bone flap was removed over the frontal necortex by drilling two lines parallel to bregma, one immediately anterior to bregma and the other 4.5 mm anterior to bregma. These two lines were connected by two more that extended in the anterior–posterior direction along the most lateral portions of the exposed skull. The frontal cortex was ablated by aspiration under visual guidance. When the lesion was completed, oxidized cellulose (Oxycel; Parke, Davis) was placed into the wound to aid coagulation. The bone flap was replaced, and pieces of Gelfoam (Upjohn) were used to fill in the gaps produced by drilling. The region of skull was coated with dental acrylic and allowed to dry. The incision was closed with autoclips. Half of the rats received sham operations, which consisted of removing the bone flap from the skull without damaging the cortex. The bone flap was replaced as described for the lesion operation. A relatively short postoperative recovery period (24–30 hr) was used in these studies because frontal cortex lesions have been shown to induce aphagia (Kolb, 1984), and food deprivation alone has been shown to elicit hypogalgesia (Ham, Kinsel, Watson, Lyeth, & Bosut, 1985; McGovern, Berke, Bernson, Walker, & Sandman, 1979).

Shortly after behavioral testing, rats were deeply anesthetized with ether and perfused intracardially with saline followed by a 10% Formalin solution. After fixation, the brains were sliced in the sagittal plane into 50- to 75-μm sections. Approximately every 10th section was mounted and stained with thionine. The extent of the frontal lesion was determined by microscopic examination and reconstructed on standard atlas plates. Figure 1 depicts a representative lesion at three medial to lateral levels (1.4, 2.4, and 3.4).

Apparatus

During behavioral testing, the rats were restrained in Plexiglas tubes (22 cm long, 6.8 cm in internal diameter). Tailshock was provided by a 660-V transformer that produced a constant-current 1.0-mA shock. The shock electrode was constructed from a modified fuse clip that was coated lightly with electrode paste. The electrode was taped to the rat’s tail, approximately 15 cm behind the rear of the tube. Pain responsiveness was assessed with the radiant-heat tailflick test. A detailed description of this device, as well as other details of the apparatus, can be found elsewhere (Grau, 1987a, 1987b; Meagher et al., in press).

Experiment 1: The Effect of Frontal Cortex Lesions on Hypogalgesia Induced by Brief and Long Shocks

In this experiment, we examined the impact of a frontal cortex lesion on the hypogalgesia observed after exposure to brief shocks or long shocks. We chose to focus on this region for several reasons. First, lesions of this region spare much of the forebrain, which should minimize the degree to which the lesion affects other physiological systems. Indeed, lesions of frontal cortex often have little impact on behavior in various tasks (Kolb, 1984). Second, anatomical evidence (Basbaum & Fields, 1984) indicates that the frontal cortex could exert descending control over midbrain nuclei known to be involved in pain inhibition (Basbaum & Fields, 1984; Hardy & Leichnetz, 1981; Mantyh, 1983). Third, electrophysiological and stimulation studies indicate that the prefrontal cortex may modulate the activity of the midbrain analgesic systems. Supporting this hypothesis, Hardy and Haigler (1985) have shown that prefrontal cortex stimulation influences the firing rates of nociceptive neurons in the midbrain. Moreover, Hardy (1985) reported that electrical stimulation of the prefrontal cortex elicits a strong hypogalgesia.

Method

Twenty-four to 30 hr after they had received a frontal cortical lesion or a sham operation, the rats were placed in the restraining tubes and given 15 min to acclimate. All of the subjects then received four tail-flick tests at 2-min intervals to establish baseline levels of pain reactivity. To prevent tissue damage, an 8-s cutoff was used. The last three trials were averaged to provide a measure of the rats’ baseline tail-flick latency. Immediately after baseline testing, the shock electrodes were attached to the rats’ tails with adhesive tape. The complete experiment involved a 2 (Operation) x 3 (Shock Condition) factorial design. Immediately after the last baseline tailflick latency test was assessed, the subjects were randomly assigned to one of three shock conditions. Ten of the lesioned and sham-operated subjects received three 25-s, 1.0-mA shocks spaced 20 s apart (long-shock groups). Another 10 of the lesioned and sham-operated subjects received three 0.75-s, 1.0-mA shocks spaced 20 s apart (brief-shock groups). The last 10 lesioned and sham-operated animals served as unshocked controls (unshocked groups). The last group of subjects were treated the same way as the others, with the exception that the shock was withheld. After the last shock, or an equal period of restraint for the unshocked groups, the shock electrodes were removed, and five tail-flick trials were administered at 2-min intervals.

Results

The baseline scores revealed no significant differences among the groups before shock treatment (all Fs < 1.0, p > .05; Figure 2, Panel A). The postshock data indicated that exposure to brief or long shocks induced a strong hypogalgesia in sham-operated subjects. In contrast, only long shocks elicited hypogalgesia in the lesioned rats. These impressions were confirmed by statistical analyses. Because the trials effect did not interact significantly with the between-subject treatments, the data were collapsed across the five postshock test trials. An analysis of variance (ANOVA) verified that shock had a significant effect on pain reactivity, F(2, 54) = 12.9, p < .001. The main effect of the operation was not significant, F(1, 54) = 0.02, p > .05. Most important, the interaction term revealed that the effect of shock depended on whether the rats had received a lesion, F(2, 54) = 5.66, p < .01.

Post hoc comparisons with the Newman-Keuls test (p < .05) verified that both of the sham-shocked groups were hypoalgesic relative to the unshocked sham group. In addition,
the sham group that received brief shocks was also hypoalgesic compared with the lesioned groups that received brief shocks or remained unshocked. The lesioned group that received long shocks was hypoalgesic relative to the lesioned group that received brief shocks and to both of the unshocked control groups. No other significant differences existed. Thus, brief shocks and long shocks induced a significant hypoalgesia in sham-operated subjects. Frontal cortex lesions blocked the hypoalgesia observed after brief shocks but not long shocks.

Experiment 2: The Effect of Sham Surgery on the Form of Hypoalgesia Induced by Brief Shocks

In previous work, Grau (1984, 1987a) showed that the brief-shock schedule that we used in the set of experiments elicits a transient nonopioid hypoalgesia and a prolonged opioid hypoalgesia. In Experiment 1, we showed that the hypoalgesia induced by brief shocks is blocked by frontal cortex lesions, and in other studies, we have shown that the hypoalgesia is also blocked by decerebration (Meagher et al., in press). These findings suggest that forebrain systems play an essential role in mediating the nonopioid and the opioid hypoalgesia observed after mild shock.

Recently, a different perspective has been suggested by Maier (1989). Although Maier agrees that forebrain systems can play a crucial role in activating the opioid hypoalgesic systems, he denies that forebrain systems play an essential role in activating the nonopioid hypoalgesic systems. Instead, he suggests that the nonopioid hypoalgesic systems can be activated only directly, at the level of the brainstem or spinal cord. Contrary to his proposal, the results of Experiment 1 suggested that forebrain systems play a role in activating the nonopioid hypoalgesic systems. However, it could be argued that our sham operation, per se, eliminated the nonopioid hypoalgesia. Indeed, Watkins et al. (1984) provided evidence that a sham operation can have exactly this impact. The purpose of Experiment 2 was to determine whether the form of the hypoalgesia elicited by the brief shock is influenced in this way by the stress of the sham surgery.

Method

All of the subjects received a sham operation as described above. Twenty-four to 30 hr after the operation, the subjects were assigned randomly to one of four groups (n = 8). Half of the rats received an injection of naltrexone (14 mg/kg s.c.). The remaining half received saline injections. After the injection, the subjects were placed in the restraining tubes, where they acclimated for 15 min. The baseline and postshock tail-flick testing procedures were the same as described in Experiment 1. Half of the rats in each drug condition received three 0.75-s, 1.0-mA shocks spaced 20 s apart. The remaining half were treated the same way, except that shock was withheld.

Results

Comparison of the baseline latencies reveals that the four groups did not differ before shock treatment (Fs < 1.0, p > .05; Figure 2, Panel B). Inspection of the postshock data reveals that shock induced a strong hypoalgesia in saline-treated subjects. The hypoalgesia lasted the entire 10 min of testing. By contrast, naltrexone-treated subjects appeared hypoalgesic at 2 min after shock, but not at 4–10 min after shock. The between-subjects terms of an ANOVA confirmed that shock, F(1, 28) = 21.98, p < .001, and drug treatment, F(1, 28) = 4.86, p < .05, had a significant impact on pain reactivity. Most important, the interaction term confirmed that the impact of shock depended on drug treatment, F(1, 28) = 5.06, p < .05.

The within-subjects terms of the ANOVA revealed a significant trials effect, F(4, 112) = 12.91, p < .001, and Trials × Shock interaction, F(4, 112) = 6.10, p < .001. The three-way interaction between shock, drug, and trials was marginally significant, F(4, 112) = 2.02, p < .10. The Trials × Drug interaction did not approach significance, F(4, 112) = 0.87, p > .05.

On the basis of prior work (Grau, 1984, 1987a), we anticipated that naltrexone would have little impact on the hypoalgesia observed 2 min after shock and fully block the hypoalgesia observed 6–10 min after shock. These results allowed us to construct a contrast, a priori, to compare the levels of pain reactivity observed 2 min after shock with those observed 6–10 min after shock. This contrast (3, 0, −1, −1,
-1) was then used to further analyze each of the within-subjects terms. With this contrast, we obtained a significant trials effect, $F(1, 112) = 49.43$, $p < .001$, and Trials × Shock interaction, $F(1, 112) = 22.46$, $p < .001$. The Trials × Drug interaction was not significant, $F(1, 112) = 0.051$, $p > .05$.

Most important, the application of this contrast to the three-way interaction revealed that the levels of pain reactivity observed at 2 min versus with 6–10 min after shock depended on shock and drug treatment, $F(1, 112) = 5.55$, $p < .05$.

Post hoc comparisons with the Newman-Keuls test revealed that 2 min after shock, the two shocked groups were hypoalgesic relative to both of the unshocked groups ($p < .01$). At that point, no other differences approached significance. Six to 10 min after shock, the saline-treated shocked subjects were hypoalgesic relative to the other three groups ($p < .01$). No other differences were significant.

Thus, brief shock elicited a transient nonopioid and a prolonged opioid hypoalgesia in sham-operated subjects. This result fits the pattern of data previously observed in intact subjects. Thus, in contrast to Watkins et al. (1984), the sham

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**Figure 2.** Preshock and postshock tail-flick latencies. (Panel A: Mean tail-flick latencies from Experiment 1. Subjects received brief shocks [B], long shocks [L], or no shock [U]. The left graph depicts the results from the sham-operated subjects, and the right graph depicts the results from subjects that received frontal cortex lesions. Panel B: Mean tail-flick latencies from Experiment 2. Subjects received brief shocks [B] or remained unshocked [U]. The left graph depicts the results from subjects that had received saline, and the right graph depicts the results from naltrexone-treated subjects. Baseline levels of pain reactivity are depicted in the left corner of each graph. The levels of pain reactivity observed after shock, or an equivalent period of restraint, are presented on the right side of each graph.)
operation we used appears to have relatively little impact on the form of the hypoalgesia observed after brief shock. There are several reasons our sham operation per se may have less of an impact. First, our subjects were given 24–30 hr to recover, whereas Watkins et al. allowed just 10–12 hr for recovery. Second, our sham operation was probably less traumatic because it required removing only a relatively small portion of the skull.

Discussion

In this study, we evaluated the role of the frontal cortex in hypoalgesia induced by brief and long shocks. Although anatomical and physiological data suggested that this structure may modulate the activity of the brainstem hypoalgesic systems, no functional evidence has been provided. Experiment 1 provided the first behavioral demonstration that the frontal cortex mediates the activation of the hypoalgesic systems when mild shocks are experienced. Specifically, we showed that a lesion of this structure eliminates the hypoalgesia normally observed after exposure to mild shocks. In contrast, the lesion had no impact on the hypoalgesia observed after severe shock.

The overall pattern of results fits well with our previous work. In other research, we have demonstrated that both pentobarbital anesthesia and decerebration block the hypoalgesia observed after brief shocks but not long shocks (Grau, 1987a; Meagher et al., in press). In this regard, frontal cortex lesions appear to have an identical impact. However, the pattern of results observed after frontal cortex lesions and after pentobarbital anesthesia differ in one way from the pattern observed after decerebration: Unlike pentobarbital anesthesia and frontal lesions, decerebration appears to potentiate the hypoalgesia observed after long shocks. There are two possible interpretations of these divergent findings. One possibility is that structures caudal to the frontal cortex are involved in the inhibition of brainstem systems. Alternatively, the potentiation effect may be an artifact of the unstable physiological state of decerebrate subjects.

In Experiment 2, we examined the impact of the sham operation on the hypoalgesia elicited by brief shock. We found that brief shock elicited the same pattern of results in sham-operated subjects as is normally observed in intact subjects: a transient nonopioid hypoalgesia followed by a prolonged opioid hypoalgesia. Because frontal cortex lesions entirely eliminated the hypoalgesia observed after mild shock, these results suggest that the frontal cortex plays an essential role in activating both the opioid and nonopioid hypoalgesic systems in this situation.

These findings pose problems for other researchers (Maier, 1989) who have suggested that forebrain systems influence only the opioid form of hypoalgesia. According to Maier (1989), all instances of nonopioid hypoalgesia reflect the "passive" activation of the brainstem or spinal cord hypoalgesic systems, what we refer to as "direct activation." However, in this study and elsewhere (Grau, 1987a; Meagher et al., in press), we have provided considerable evidence that forebrain systems may also mediate the activation of nonopioid hypoalgesic systems. We have provided three converging lines of evidence as support: Deep pentobarbital anesthesia (Grau, 1987a), decerebration (Meagher et al., in press), and frontal cortex lesions, have all been shown to attenuate or eliminate the nonopioid hypoalgesia observed after brief shocks.

References


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