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BRIEF COMMUNICATION

Role of Contextual Stimuli in Tolerance to Stress-Induced Analgesia

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BLUSTEIN, J. E., G. HORNIG AND M. BOSTWICK-POLI. *Role of contextual stimuli in tolerance to stress-induced analgesia.* PHARMACOL BIOCHEM BEHAV **52**(4) 841-844, 1995.—The present study was conducted to determine whether tolerance to stress-induced analgesia was mediated by contextual cues. Following baseline measurement of analgesia using a tail curl test, rats were exposed to nine sessions of 30 min of intermittent inescapable shock (tolerance development phase) in which one half of the rats began in context A and the other half in context B. A tail-curl test immediately followed each shock session. On the 10th day, 4 days after tail-curl latencies returned to baseline, the contexts were switched, and the rats were exposed to the same shock parameters as before. The results revealed a significant increase in tail-curl latency when the context was switched compared with the last day of the tolerance development phase. These data suggest that tolerance to stress-induced analgesia may at least in part be associatively mediated by the context.

Stress-induced analgesia Tolerance Context

IT HAS BEEN widely reported in the literature that rats exposed to uncontrollable stressors exhibit decreased sensitivity and reactivity to pain. Several important findings have been reported that characterize this phenomenon. For instance, stress-induced analgesia (SIA) has been found to be mediated by either opioid or nonopioid substrates depending on the characteristics of the stressor (7,8), the analgesia can be conditioned according to the principles of Pavlovian conditioning (4), tolerance to analgesia has been demonstrated (3), and behaviors associated with opioid withdrawal can be precipitated by the opioid antagonist naltrexone (4,5).

One important parallel reported between some forms of opioid-mediated SIA and morphine analgesia is the development of tolerance. For example, repeated exposure to 20-min sessions of intermittent inescapable shock leads to a failure of the same nominal intensity of the shock to produce analgesia (9).

It is widely accepted in the literature that tolerance to morphine analgesia is associatively mediated (12,14). In a classic study (12) rats were injected with morphine over successive days and the resulting analgesia progressively diminished, suggesting the development of tolerance. During the test, the same dose of morphine was given in either the original or a new environment. The results showed that those animals that were tested in the new context were analgesic, whereas rats tested in the original context continued to exhibit tolerance to analgesia. Thus, when contextual stimuli associated with the drug injection ritual were changed, injection of the drug once again produced analgesia.

Recently, it has been demonstrated that tolerance to the hypothermic consequences of cold-water swims is associatively mediated through Pavlovian processes (10). These data widen the domain in which Pavlovian conditioning can have a role in the development of tolerance to include nondrug effects.

Despite wide acceptance that tolerance to morphine analgesia is at least in part associatively mediated by the context through Pavlovian conditioning [(12-14,15); see (1) for a review of an alternative theoretical framework], there is no empirical evidence that tolerance to SIA is also associatively mediated by the context.

The present study extends previous research (10,12-14) to determine whether tolerance to a form of SIA known to have an endogenous opioid substrate (6,7) is also, at least in part,

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mediated by the context. Rats were subjected to a total of nine 30-min inescapable shock sessions in which they received 1.5-mA shocks for 2 s with a 4-s intershock interval in either of two contexts. On day 10 the contexts were switched, and the rats were once again subjected to the same shock conditions that prevailed throughout the preceding nine sessions. Analgesia was tested using a tail-curl test in which the rat's tail was immersed into warm water and the latency to remove the tail was recorded.

METHOD

Subjects

The subjects were 10 adult male Long-Evans rats, 150 days old at the start of the experiment. The rats were bred in the Beaver College animal facility and housed individually with free access to food and water for the duration of the experiment. The rats run in Context A were maintained on a 12-h reverse light-dark cycle. The rats run in Context B were maintained in the dark.

Apparatus

We used a 3000-ml beaker filled with water for measuring tail-curl latencies. The water was heated with a Thermolyne Corp. (Dubuque, IA) hot plate (model HP-A1915B). Voltage to the hot plate was regulated by a powerstat (type 116) manufactured by Superior Electronics (Bristol, CT). The water temperature was monitored using an AHT Fisher Scientific (Pittsburgh, PA) centigrade thermometer. A stopwatch, manufactured by Fisher Scientific (Pittsburgh, PA), was used to time tail-curl latencies. During the analgesimetric test, the rats were placed in a cloth cone-shaped restraining device with a 1-cm hole in the point through which the tail was threaded.

Context A consisted of a modified Skinner box that measured 33 × 23 × 14 cm, and which was kept dark during the tolerance acquisition phase of the experiment. The front wall was constructed of stainless steel and the back and side walls were constructed of Plexiglas. No manipulanda were present in the chamber. The floor of the chamber consisted of stainless-steel metal grids that were 1 cm in diameter and spaced 1.5 cm apart, center to center. The Skinner box was enclosed in a sound- and light-attenuating chamber. Several extrachamber contextual stimuli were present in Context A. Red lights were used in the laboratory (25 W) to maintain a dark environment. In addition, a radio was played at 67 dB. Subjects in Context A were housed in the animal room during the tolerance acquisition phase to create transportational stimuli that were different from animals in Context B.

There were several important differences between Contexts A and B. Context B consisted of a considerably smaller, modified shuttle-box, with an enclosure in which the rat was placed, measuring 23 × 10.5 × 8.5 cm. The front and back walls consisted of metal, and the side walls and top consisted of Plexiglas. In addition, the floor consisted of stainless-steel grids that measured only 0.1 cm in diameter and were spaced only 0.12 cm apart, center to center, providing very different tactile stimuli than Context A. During training the rats were exposed to a synchronized flashing light and buzzer that occurred at a rate of once/s. The modified chamber was enclosed in a light- and sound-attenuating shell. Extrachamber stimuli consisted of a lighted lab room with no music. Transportational stimuli were also different for subjects in Context B. In contrast to Context A, the rats were housed in a dark room immediately across from the laboratory. In both context conditions, shocks were delivered using a Coulbourn Instruments model E13-16 solid-state shocker/distributor (Lehigh Valley, PA). All shocks were timed and delivered by relay equipment located in the same room.

Procedure

Before the start of the experiment, the rats were handled for 5 min/day for 1 week. Prior to the shock sessions, baseline measures of pain sensitivity and reactivity were obtained using a tail-curl test in which the tail was immersed in warm water (52°C) and the latency of the tail to curl out of the water was recorded [see (6) for a review of this procedure]. Analgesia testing was conducted in the same room in which the animals were trained and tested. Subjects were placed in a loosely fitting restraint, and a trial began by holding the rat over a 3000-ml Pyrex beaker filled with the water, submerging the rat's tail 8 cm (measured from the tip of the tail) into the beaker, and simultaneously starting a stopwatch at the point when the rat's tail was completely submerged to the 8-cm mark. At the point when the rat's tail was completely removed from the water, the stopwatch was stopped, indicating the occurrence of a tail-curl response. Failure to remove the tail within 20 s terminated a trial, and a maximum latency of 20 s was recorded. Three such trials were spaced 1 min apart. Following baseline testing, one half of the animals were randomly assigned to Context A and the other half were assigned to Context B. A session consisted of 30 min of intermittent shock (1.5 mA), 2 s on, 4 s off occurring in the context. During the tolerance acquisition phase, animals exposed to shock in Context A were always transported from the animal room to the lab, whereas animals exposed to shock in Context B were always transported from the dark room across from the lab to the lab. A test of analgesia was conducted immedi-

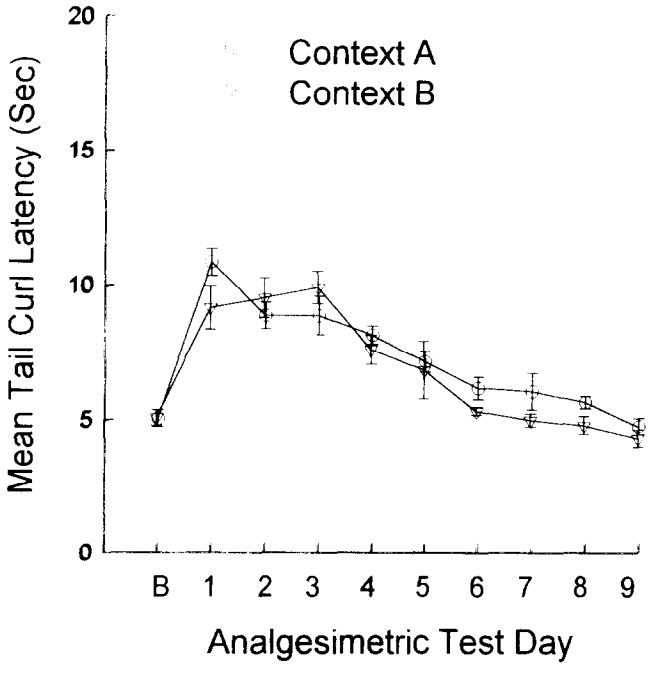

FIG. 1. Mean tail-curl latency as a fuction of test day and context. Bars represent standard errors. No significant differences were found between Context A and Context B.

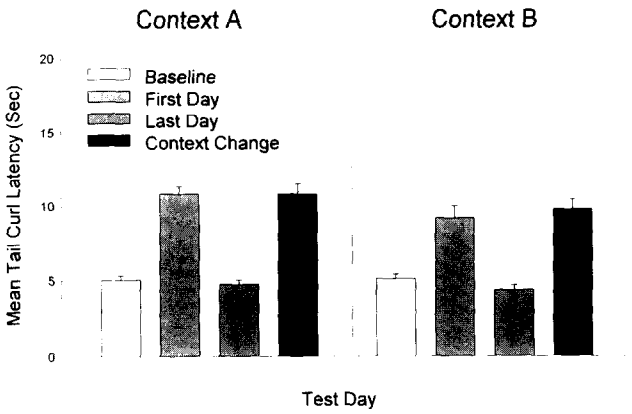

FIG. 2. Mean tail-curl latency as a function of baseline, 1st day after shock, last day after shock, and the context change test condition for Contexts A and B. Post hoc analysis revealed that irrespective of context a reliable increase in mean tail-curl latency was found from baseline to the 1st test day. Tail-curl latencies did not reliably differ from the last day to baseline and significantly increased following the context switch.

ately after each shock session. At the end of the ninth shock session animals were switched to the opposite housing environment for 24 h, followed by a single session of shock exposure in the alternative context. With the exception of the contextual change, the rats were exposed to an identical 30-min shock session. Immediately following the session, the rats were again given three tail-curl tests to assess analgesia.

RESULTS

Figure 1 illustrates the mean tail-curl latencies at baseline and across days of shock administration as a function of context. As can be seen, a substantial and equivalent increase in tail-curl latencies was observed after the first shock session for subjects in both contexts. Tail-curl latencies decreased over sessions and, by day 6, had returned to baseline to remain at these levels through the ninth session.

Figure 2 shows the mean tail-curl latencies for subjects in Contexts A and B during baseline, 1st day, last day, and context change. It is evident from these data that tail-curl latency was not differentially affected by context. Tail-curl latency increased from baseline following the first shock session and returned to baseline by the last shock session. When the contexts were switched and the rats were again shocked using the same parameters as the previous day, tail-curl latency increased to the same point as on the 1st day.

These casual observations were confirmed by a 2 × 4 split-plot analysis of variance, which revealed a reliable main effect for test day [$F(3, 24) = 78.70, p < 0.0001$]. Neither the main effect for context nor the interaction between context and day of analgesimetric testing approached significance ($p > 0.10$). The α level for all posthoc tests was set at ($p < 0.01$). Newman-Keuls post hoc tests revealed a reliable increase in tail-curl latencies from baseline to 1st day postshock. By day 9, the day before the context switch occurred, tail-curl latencies were not significantly different from baseline. In contrast, a reliable increase in tail-curl latencies was observed from last day postshock measurement to context change postshock measurement. Finally, a reliable decrease in tail-curl latency was observed from 1st day postshock assessment to last day postshock.

DISCUSSION

Immediately following the 1st day of exposure to intermittent inescapable shock, rats exhibited pronounced analgesia. These data are consistent with other reports using similar shock parameters [e.g., (8)]. The analgesia returned to basal levels after six 30-min shock sessions and remained at these levels through nine sessions. When the animals were switched to a novel context on the 10th day and exposed to identical shock parameters, pronounced analgesia was again observed at levels equivalent to those observed immediately after 1st day of shock exposure. There is considerable evidence that tolerance to morphine analgesia is at least in part under the control of contextual stimuli via Pavlovian processes [e.g., (14)]. Data from the present experiment provide strong evidence that tolerance to SIA can likewise be brought under the control of the context through associative processes.

An important question arising from these data concerns whether the contextual control of tolerance is the result of repeated activation of endogenous opiates. Although the present study did not specifically address this question, several lines of evidence suggest that this may be a viable interpretation. First, it has been demonstrated that analgesia activated by intermittent inescapable shock similar to that used in the present experiment is opioid mediated (7,8). Second, cross-tolerance between extended intermittent inescapable shock (similar to what was used in the present experiment) and the administration of morphine has also been documented (9). Taken together, these findings suggest that the contextually mediated tolerance to the form of SIA engendered by the shock parameters of the present experiment may also be the consequence of repeated activation of endogenous opiates, similar to what is observed when morphine is repeatedly injected.

In conclusion, data from the present study suggest that tolerance observed from repeated activation of endogenous opiates resulting from protracted exposure to a stressor may be controlled by contextual stimuli (through Pavlovian conditioning) in a manner similar to the way in which tolerance to exogenous opiates occurs. These data extend the finding that nondrug-based phenomena can also come under the control of contextual stimuli (10).

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