Activation of the Opioid and Nonopioid Analgesic Systems: Evidence for a Memory Hypothesis and Against the Coulometric Hypothesis

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It has been suggested that the magnitude and form of hypoalgesia elicited by an aversive event can be predicted from its coulometric product (Intensity × Duration). According to this hypothesis, small products elicit opioid hypoalgesia, and large products elicit nonopioid hypoalgesia. This suggests that increasing the duration of an aversive event should heighten the nonopioid hypoalgesia. Contrary to this prediction, in Experiment 1 I found that increasing the duration of a mild shock attenuated the nonopioid hypoalgesia. In Experiment 2 I tested another implication of the coulometric hypothesis, namely, that mild shocks that have the same coulometric product should elicit equivalent hypoalgesia. The results did not support this prediction. We discuss how these findings are consistent with an alternative theory, the “working memory hypothesis.” According to this theory, the representation of an aversive event in working memory elicits hypoalgesia. In Experiment 3 a novel prediction of this theory was tested, namely, that displacing the representation of intense shock from working memory by following the intense shock with a weak shock “distractor” would attenuate hypoalgesia. The results support this prediction. I conclude by discussing the relation of this work to other findings in the analgesia literature.

Exposure to a variety of aversive stimuli can elicit a strong hypoalgesia in rats (for reviews see Basbaum & Fields, 1984; Kelly, 1986; Terman, Shavit, Lewis, Cannon, & Liebeskind, 1984; Tricklebank & Curzon, 1984; Watkins & Mayer, 1982). Under some conditions, this hypoalgesia appears to be “opioid” in nature, because it is attenuated by opiate antagonists (e.g., naltrexone and naloxone) and morphine tolerance (Drugan, Grau, Maier, Madden, & Barchas, 1981; Lewis, Cannon, & Liebeskind, 1980; Lewis, Sherman, & Liebeskind, 1982; Maier et al., 1980; Watkins & Mayer, 1982). However, under other conditions, the hypoalgesia appears to be “nonopioid” in nature, because it is not affected by these manipulations (Chance, 1980; Lewis et al., 1980, 1982; Watkins & Mayer, 1982). These analgesic systems have received considerable attention because they may provide a means to control pain in the clinical setting. These systems are also of interest because they may mediate a variety of behavioral phenomena (e.g., habituation and conditioned diminution of the unconditioned response). However, in order to use these systems in the clinical setting and to understand their role in behavioral phenomena, we need to know the conditions under which these systems are activated. A number of hypotheses have been proposed to address this issue (Fanselow, 1984; Grau, 1986, 1987; Grau, Hyson, Maier, Madden, & Barchas, 1981; Lewis et al., 1980; Maier, Drugan, & Grau, 1982; Maier, Sherman, Lewis, Terman, & Liebeskind, 1983; Terman et al., 1984; Watkins & Mayer, 1982). The present article contrasts a theory we have proposed (Grau, 1986, 1987) with an alternative account, the “coulometric hypothesis” (Fanselow, 1984; Terman et al., 1984).

Working Memory Hypothesis

The theory proposed here posits that the central representation of an aversive event in working memory activates both the opioid and nonopioid analgesic systems (Grau, 1986, 1987). I refer to this theory as the working memory hypothesis. This basic hypothesis has been formalized by coupling it to a detailed model of learning and memory, SOP (Wagner, 1981. This model is called SOP because it is designed to capture the standard operating procedures of memory systems.) Because an understanding of our memory hypothesis requires some knowledge of SOP, I will first briefly outline the basic properties of SOP (for detailed discussions of SOP, see Donegan & Wagner, in press; Mazur & Wagner, 1982; or Wagner, 1981).

Overview of SOP

According to the SOP model, memory is a network of nodes that represent stimulus events. The nodes are connected by directional links that encode associative relations. It is assumed that the nodes are composed of “informational elements.” This aspect of the model is important because it allows for nearly continuous variation in the degree to which a node is in any one of the three memory states: “A1,” “A2,” or inactive. The A1 and A2 states correspond to active nodes in working memory;
the A1 state corresponds to the focal portion of working memory; the A2 state corresponds to the peripheral portion of working memory. It is assumed that both the A1 and A2 states have a limited capacity and that the capacity of the A2 state is much larger than the capacity of the A1 state.

A summary of the allowed state transitions is presented in Figure 1. The presentation of a stimulus activates the node it represents from the inactive state to the A1 state. The degree to which the node is activated to the A1 state depends upon the duration and intensity of the stimulus event. It also depends on the current state of the node; that portion of the node which is already in the A1 or A2 state will be unaffected by the presentation of the stimulus. According to SOP, nodes decay from the A1 state to the A2 state. Nodes can also enter the A2 state by being associatively activated. Nodes decay from the A2 state to the inactive state.

According to SOP, the nodes are interfaced to a response generator that is sensitive to whether a node is activated and to its state of activation (A1 or A2). This latter characteristic allows the system to generate different responses, depending upon whether a node is in the A1 or the A2 state.

Application

My basic hypothesis is that the active representation of an aversive event in working memory activates the opioid and non-opioid analgesic systems. It is assumed here that the magnitude of hypoalgesia is a function of the hedonic value of the representation—the more aversive the representation, the stronger the hypoalgesia. Given this basic hypothesis, we have argued that the nonopioid and opioid hypoalgesic responses must be tied to different levels of memory activation; the nonopioid hypoalgesia is generally observed when the memory of the aversive event is quite strong, whereas the opioid hypoalgesia can be observed when the memory is relatively weak. These casual notions can be formalized in terms of SOP. Specifically, we have suggested the nonopioid hypoalgesic response is tied to the A1 state and that the opioid hypoalgesic response is tied to the A2 state.

I have shown (Grau, 1986, 1987) that these assumptions allow us to accommodate a wide range of findings in the analgesia literature. Moreover, the system has the unique ability to predict not only the form of hypoalgesia but also its time course.

For example, SOP enables one to anticipate that exposure to brief shock will activate the representation of shock to the A1 state. Upon shock termination, the representation will rapidly decay from the A1 state to the A2 state, because the A1 state has a very limited capacity. Because the A2 state has a much larger capacity, decay from the A2 state to the inactive state will be considerably slower. According to our application of SOP, these state transitions should produce a transient nonopiod hypoalgesia, followed by a long-lasting opioid hypoalgesia. These predictions fit well with the time course of opioid and nonopioid hypoalgesia actually observed (Grau, 1984, 1987).

Because the A1 and A2 states have a limited capacity, information can be displaced from them by the presentation of distracting stimuli. This suggests a relatively unique prediction: We should be able to attenuate the nonopioid and opioid hypoalgesia by presenting a postshock distractor. Elsewhere (Grau, 1986, 1987), I have shown that a postshock distractor does attenuate both forms of hypoalgesia. In the present series of experiments, I evaluate a number of other predictions made by my application of SOP.

The Coulometric Hypothesis

An alternative account proposes that a simple coulometric relation (Intensity × Duration) determines whether an opioid or nonopioid hypoalgesia will be observed (Fanselow, 1984; Terman et al., 1984). Two versions of this "coulometric hypothesis" have been suggested. One version, proposed by Terman et al. (1984), simply assumes that the analgesic systems are activated by painful stimuli. According to this model, the degree to which the analgesic systems are activated depends upon the severity of the aversive event, which is determined by a coulometric relation. This hypothesis can be used to predict the form of hypoalgesia observed by assuming that the coulometric product required to activate the opioid analgesic system is much lower than the product required to activate the nonopioid analgesic system.

A slightly different version of the coulometric hypothesis has been suggested by Fanselow (1984). This version builds upon the perceptual-defensive-recovery (PDR) theory proposed by Bolles and Fanselow (1980). In contrast to the account suggested by Terman et al. (1984), PDR theory rejects the assumption that noxious stimuli directly activate the analgesic systems and assumes instead that conditioned fear mediates their activation. Specifically, it is proposed that animals associate the aversive event to the context in which it occurred. This association arouses a state of fear, which, in turn, elicits hypoalgesia (Bolles & Fanselow, 1980). In the original form of PDR theory, Bolles and Fanselow simply assumed that conditioned fear elicits an opioid hypoalgesia. However, it subsequently became clear that the hypoalgesia observed in some situations is mediated by a nonopioid system. It was therefore necessary to append PDR theory with postulates that would allow it to predict whether an hypoalgesia would be opioid or nonopioid in nature. Fanselow (1984) has addressed this issue by suggesting that whether conditioned fear elicits an opioid or nonopioid hypoalgesia depends upon the severity of the unconditioned stimulus, which, in turn, is determined by a coulometric relation. Like Terman et al., Fanselow assumed that stimuli which have a
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small coulometric product elicit an opioid hypoalgesia and that increasing the coulometric product increases the degree to which the nonopioid analgesic system is activated.

Experimental Predictions

Although there are a variety of differences between the coulometric hypotheses proposed by Fanselow (1984) and Terman et al. (1984), both accounts make similar predictions if algesia is assessed immediately after the aversive event in the same context as the event occurred. For example, in this situation both accounts anticipate that we should be able to increase the magnitude of the nonopioid hypoalgesia elicited by a brief shock by increasing shock duration. In addition, both versions anticipate that shocks that yield the same intensity (measured in mA) at times duration product should yield equivalent hypoalgesia. These two predictions are tested in Experiments 1 and 2. Interestingly, I will show that our working memory hypothesis anticipates that these manipulations may have a quite different impact. In the last experiment, a novel prediction of our working memory hypothesis is tested, namely, that I should be able to attenuate the hypoalgesia elicited by an intense shock by following the intense shock with a weak shock “distractor.”

Experiment 1

In this experiment the impact of increasing the duration of an aversive event on the form and the magnitude of hypoalgesia is tested. This is accomplished by exposing animals to no shock (unshocked), a brief 20-s (0.25-mA) shock (brief shock), or a long 80-s (0.25-mA) shock (long shock). In order to disentangle the impact of this manipulation on the opioid and nonopioid components of hypoalgesia, animals were treated with either saline or naltrexone (an opioid antagonist) prior to shock treatment. The impact of duration on the net hypoalgesia (opioid + nonopioid) will be evident from a comparison of the saline-treated groups; the impact of duration on the nonopioid hypoalgesia will be evident from a comparison of the naltrexone-treated groups.

The shock parameters were chosen on the basis of pilot work which had revealed that the brief shock induced both a transient nonopioid hypoalgesia and a long-lasting opioid hypoalgesia. In terms of the coulometric hypothesis, the fact that the brief shock elicits both forms of hypoalgesia suggests that it is close to the threshold product required to observe a nonopioid hypoalgesia. Given this, the coulometric hypotheses anticipates that increasing shock duration should increase the magnitude of the nonopioid hypoalgesia observed in naltrexone-treated subjects. It might also be anticipated that increasing the magnitude of the nonopioid hypoalgesia will augment the net hypoalgesic response observed in the saline-treated subjects.

Under some conditions, my theory also anticipates that increasing the duration of an aversive event will increase the magnitude of the nonopioid hypoalgesia. This will occur if an aversive event is so brief that it only weakly activates its representation to working memory. In this situation, increasing the duration, or intensity, of the aversive event will increase the degree to which its representation is activated to the focal portion of working memory and, hence, the magnitude of the associated nonopioid hypoalgesia. However, my theory suggests that under other conditions, an increase in the duration, or intensity, of an aversive event may have a quite different impact on algesia. For example, let us assume that the brief shock used in the present experiment is strong enough to nearly fully activate its representation to working memory (some evidence for this claim will be provided in Experiment 3). In this case my theory suggests that an increase in intensity, or duration, will attenuate the nonopioid hypoalgesia rather than augment it. The reason for this is that after the representation is nearly fully activated to working memory by the brief shock, there will be little of the node remaining in the inactive state to be activated to the A1 state. Hence, further increases in shock duration will add little to the A1 state. Because of this, the representation will begin to decay from the A1 state to the peripheral A2 state much faster than it is replaced. This will produce a decrease in the proportion of the node in the A1 state and a concomitant increase in the proportion of the node in the A2 state. According to our application of SOP, this redistribution of the representation will have a number of important consequences. First, a decrease in the proportion of the node in the A1 state should produce a decrease in the nonopioid hypoalgesia observed in naltrexone-treated subjects. Secondly, the increase in the proportion of the node in the A2 state should heighten the magnitude of the opioid hypoalgesia observed immediately after shock termination. Finally, the fact that the node will be primarily in the A2 state upon shock termination will give the node a bit of a “head start” toward decaying back to the inactive state. Oddly, this suggests that the net hypoalgesia observed in the saline controls may decay more rapidly after the long shock than the brief shock.

Method

Subjects. The subjects were 60 male Sprague-Dawley rats (Charles River Laboratories). The animals were 100-120 days old and weighed between 380 g and 500 g. They were maintained on a 12-hr light/dark cycle. The subjects were individually housed and had food and water continuously available.

Apparatus. Two Plexiglas tubes were used to restrain the subjects. These tubes were 22 cm in length and had an internal diameter of 6.8 cm. Extending across the base of each tube, 5.3 cm from the top, was a 5.5-cm-wide Plexiglas sheet, which formed a stable platform on which the rat could stand. The front of the tubes was sealed with a clear Plexiglas sheet. In order to prevent the subjects from being distracted by extraneous visual stimuli, the external surfaces of the tubes were covered with duct tape. Thirteen (0.9 cm in diameter) ventilation holes were drilled through the midsection of the tubes. A band of adhesive tape was used to seal the rear of the tubes. The subject's tail protruded from the rear of tubes, between the band of adhesive tape and the base of the tubes.

A 660-V transformer, in combination with a 2.03-Mohm series resistor, was used to generate a constant-current 0.25-mA shock, which was applied to the rat's tail. The shock was delivered through electrodes constructed from a modified fuse clip. The plates of the electrode were lightly coated with electrode paste. The electrode was attached to the rat's tail, centered about 15 cm behind the rear of the tubes.

Algesia testing was conducted with a radiant heat tail-fllick device. A 375-W movie light (Sylvania, type EBR) was positioned 18 cm above the base of the apparatus. A condeaser lens was placed 8 cm below the light and served to focus the light onto the rat's tail. The rat's tail rested on an aluminum block that had an 0.8-cm-wide, 0.4-cm-deep groove...
cut into it. A photo cell, positioned below the groove, automatically terminated the trial if the rat moved its tail laterally by at least 0.5 cm. The duration of the trial was automatically timed to the nearest 0.01 s.

Testing was conducted in an isolated room that was maintained at a temperature of approximately 26.5 °C. Ventilation fans provided a background noise level of about 60 dB (SPL).

Procedure. The subjects were randomly assigned to one of six groups (n = 10). Half of the subjects were administered a subcutaneous 14-mg/kg dose of naltrexone (DuPont pharmaceuticals). This dose of naltrexone was chosen on the basis of prior work showing that it is as large, or larger than, the dose of naltrexone needed to eliminate the putative opioid hypoalgesia observed in a variety of experimental situations (Grau et al., 1981; Hyson, Ashcraft, Drugan, Grau, & Maier, 1982; Maier et al., 1980). The other subjects received its vehicle, saline. Immediately after the injection the subjects were placed in the restraining tubes and were allowed to acclimate for 15 min. The subjects were then given three tail-flick tests at 2-min intervals. An 8-s cutoff was used in order to prevent tissue damage. The last two tests were used to compute the subject's baseline level of pain reactivity. After the last tail-flick test, the electrodes were attached to the rat's tail with adhesive tape. One-third of the subjects (long shock) in each drug condition then received an 80-s, 0.25-mA shock. Another third (brief shock) experienced a 20-s, 0.25-mA shock, which was administered 60 s after the electrodes were attached. The remaining subjects (unshocked) were treated the same except that shock was withheld. Two minutes after shock termination, or an equivalent period of restraint, the rat's tail was untaped, and pain reactivity was tested five times at 2-min intervals.

Results

I found that increasing shock duration attenuated the non-opioid hypoalgesia. In addition, I observed that the hypoalgesia produced by the long shock decayed more rapidly.

The results of the experiment are depicted in Figure 2. The left panel of this figure shows the results from the subjects that received saline. The right panel depicts the results from the naltrexone-treated subjects. Baseline levels of pain reactivity are depicted on the left side of each panel. It is clear that no significant differences existed between the groups prior to shock treatment. This observation was confirmed by an analysis of variance (all Fs < 0.52, p > .05).

The right side of each panel depicts the levels of pain reactivity observed after shock treatment. Inspection of the saline-treated subjects reveals that the brief shock induced a strong and long-lasting hypoalgesia. Interestingly, although a strong hypoalgesia was observed immediately after the long shock, this hypoalgesia decayed more rapidly. The results from the naltrexone-treated subjects reveal that the brief shock induced a strong non-opioid hypoalgesia. The long shock, however, did not.

These impressions were confirmed by an analysis of variance. The between-subjects terms revealed a significant main effect of both shock, F(2, 54) = 27.61, p < .001, and drug, F(1, 54) = 7.62, p < .05, treatment. The interaction between shock and drug treatment was not significant, F(2, 54) = 2.39, p > .05. Post hoc comparisons of the group means with a Newman-Keuls test (p < .05) showed that the saline-treated shocked subjects and the naltrexone-treated subjects that experienced a brief shock were hypoalgesic relative to both the unshocked controls and the naltrexone-treated subjects that experienced the long shock. No other comparisons were significant.

The within-subjects terms revealed a significant trials effect, F(4, 216) = 13.07, p < .001. Most important, the three-way interaction showed that the change in pain reactivity observed across trials depended upon both shock and drug treatment, F(8, 216) = 2.63, p < .05. The trials effect did not interact significantly with either shock, F(8, 216) = 1.84, p > .05, or drug, F(4, 216) = 1.80, p > .05, treatment alone.

In order to clarify the nature of the three-way interaction among trials, shock, and drug treatment, I compared the level of pain reactivity exhibited by the shocked subjects at the 2- and 10-min test points. The Bonferroni t statistic was used to make these comparisons because it maintains the error rate at the .05 level (two-tailed test) for a family of contrasts (Myers, 1979). Analysis of the data from the saline treated shocked subjects showed that the long and brief shock induced a similar level of hypoalgesia at the 2-min test point (t = 0.34, p > .05). However, at 10 min after shock, significantly less hypoalgesia was observed after the long shock (t = 3.14, p < .05). Comparisons of the groups that received brief shock showed that naltrexone had little impact on the hypoalgesia observed 2 min after shock (t = 2.17, p > .05), but significantly attenuated the hypoalgesia at 10 min after shock (t = 2.97, p < .05). By contrast, comparison of the groups that received long shock revealed that naltrexone attenuated the hypoalgesia observed 2 min after shock (t = 6.66, p < .01), but had little impact at 10 min after shock (t = 0.14, p > .05). Comparison of the naltrexone-treated shocked subjects showed that significantly less hypoalgesia was observed after the long shock at the 2-min test point (t = 4.83, p < .01), and that little difference existed at the 10-min test point (t = 0.14, p > .05).

Discussion

I found that the brief shock induced a strong and long-lasting hypoalgesia in saline-treated subjects. Naltrexone had little im-
impact on this analgesia at the 2-min test point but fully blocked the hypoalgesia observed at 10 min after brief shock. This pattern of results suggests that the brief shock induced both a transient nonopioid hypoalgesia and a long-lasting opioid hypoalgesia. Increasing the duration of the shock had two important consequences. First, it produced an hypoalgesia that decayed more rapidly in saline-treated subjects. Secondly, it attenuated the nonopioid hypoalgesia observed in the naltrexone-treated subjects.

The results of this experiment were not anticipated by the coulometric hypothesis. According to this hypothesis, increasing shock duration should have increased the degree to which the nonopioid analgesic system was activated and, hence, augmented the hypoalgesia observed in both the saline- and the naltrexone-treated subjects. However, the opposite was found.

By contrast, the results are readily accommodated by the working memory theory. First, the theory correctly anticipated that hypoalgesia might decay more rapidly after the long shock. Secondly, it also predicted that increasing shock duration could undermine the magnitude of the nonopioid hypoalgesia, replacing it with an opioid mediated hypoalgesia.

**Experiment 2**

The present experiment was designed to test a basic assumption of the coulometric hypothesis. According to this hypothesis, stimuli that yield the same intensity times duration product should yield equivalent hypoalgesia. For example, one should be able to produce equal hypoalgesia in rats with 0.1-mA and 1.0-mA shocks by simply making the 0.1-mA shocks 10 times longer than the 1.0-mA shocks. The present experiment was conducted to test this prediction.

One might argue, however, that this experiment does not represent a fair test of the coulometric hypothesis because 0.1-mA shocks may be so weak that they are not aversive or even noticed. There are a number of ways we can address this issue. First, it should be noted that the study Fanselow (1984) cites to support his claim that shock severity can be described by a coulometric relation (Church, Raymond, & Beauchamp, 1967) used less intense (0.05-mA) shocks. Secondly, Experiment 1 showed that a shock that is only slightly more intense induces a strong hypoalgesia. Finally, the criticism that 0.1-mA shocks are not aversive can be addressed by providing direct evidence that rats do find this shock intensity noxious. This was accomplished by measuring the degree to which the shock induced struggling (straining against the shock electrodes) and vocalization. Considerable evidence suggests these measures provide a good index of the degree to which rats find tail-shock aversive (Carroll & Lim, 1960; Grau & Meagher, 1987; Hoffmeister, 1968). For example, I have shown that increasing shock intensity increases both vocalization and struggling and that morphine and pentobarbital attenuate vocalization and struggling in a dose-dependent fashion (Grau & Meagher, 1987).

In contrast to the coulometric hypothesis, the working memory hypothesis does not anticipate that increasing the duration of a weak shock will necessarily allow it to induce as strong a hypoalgesia as a brief intense shock. Increasing shock duration will compensate for the slow rate at which a weak shock activates its representation to working memory. Hence, it might be assumed that the weak shock activates its representation to working memory as strongly as the brief intense shock activates its own representation. However, being activated to working memory to an equivalent extent is not sufficient to produce equal hypoalgesia. Rather, I assume that an active representation will elicit hypoalgesia only if it has an aversive quality and that the more aversive the representation, the greater the hypoalgesia. In terms of SOP, I am assuming that there are featural elements that encode the degree to which a representation has a negative hedonic value. With respect to a stimulus like shock, such a difference in hedonic value might be represented by differences in the quality of the featural elements or simply by their quantity. In either case, I anticipate that decreasing the aversiveness of the shock, by decreasing its intensity, would decrease the degree to which its representation will activate the analgesic systems. Thus, the memory hypothesis anticipates that the weak shock will elicit hypoalgesia that is only a fraction of that elicited by the intense shock, provided that both shocks activate their representations to working memory to a roughly equivalent extent.

The experimental design involved three groups. One group (intense shock) of subjects experienced three 0.75-s, 1.0-mA shocks. Another group (weak shock) received three 7.5-s, 0.1-mA shocks. According to the coulometric hypothesis, these two shock conditions should produce equivalent hypoalgesia. By contrast, the working memory hypothesis anticipates that the weak shock will elicit much less hypoalgesia. The final group (unshocked) served as unshocked controls.

**Method**

**Subjects.** The subjects were 24 rats of the same age, sex, and strain as used in Experiment 1.

**Apparatus.** The apparatus used to restrain, shock, and tail-flick test was the same as that used in Experiment 1.

Vocalization was measured with a miniature microphone (Radio Shack 270-092B) that was positioned over a 9.4-mm hole. This hole was drilled through the top of the tube 2.5 cm from the front. The microphone was connected to a Sanyo amplifier (DCA 611) that was adjusted to selectivity amplify frequencies above 1500 Hz. At 80 dB, frequencies below 1500 Hz were attenuated by approximately 8 dB. The response function of the system was relatively flat (±0.5 dB) from 1500 to 20,000 Hz. The output from the amplifier was fed into a full wave rectifier. This provided a DC voltage that was proportional to the intensity of the sound pressure level at the microphone. The DC voltage was fed into an analog-to-digital converter (Alpha Products, Analog 80) that was connected to a Radio Shack Model III computer. The computer read and recorded the digital input approximately 19 times per second. This system has been calibrated by determining the relation between the digital input and the loudness of a 4000-Hz sine-wave tone. The computer used this derived function to convert each of the digital inputs to dB. Sounds below 47.1 dB were ignored. This cutoff helped to prevent extraneous sounds, such as breathing, from contaminating our vocalization data. The system could measure sounds up to an intensity of 93.5 dB.

Struggling was measured by attaching a strain gauge to the tail electrodes. The strain gauge was connected to the electrodes by a wire and was positioned 20 cm behind the electrodes. The strain gauge was constructed from a spring-loaded potentiometer. This potentiometer was connected to an adjustable voltage regulator that controlled the voltage received by the analog-to-digital converter. The output from each of the strain gauges was sampled approximately 19 times per second. This
system has been calibrated by computing the relation between the digital inputs and force in newtons. The system could measure forces up to 10 N.

Procedure. The rats were placed in the restraining tubes and allowed to acclimate for 15 min. Baseline levels of pain reactivity were then assessed, and the electrodes were attached, as described in Experiment 1. The rats were then randomly assigned to one of three groups. One group (intense shock) received three 0.75-s, 1.0-mA shocks spaced 20 s apart. Another group (weak shock) received three 7.5-s, 0.1-mA shocks spaced 20 s apart. The final group (unshocked) was treated the same except that shock was withheld. Upon shock termination, or an roughly equivalent period of restraint, pain reactivity was tested five times at 2-min intervals.

Results

I found that both the intense and weak shocks induced vocalization and straining. However, only the intense shock elicited significant hypalgesia.

In order to compare the degree to which the weak and intense shock elicited vocalization, I computed the magnitude of vocalization observed during the first 0.75 s of the shock periods. During this period the computer sampled and recorded the magnitude of vocalization approximately 15 times. These values were then used to determine the mean magnitude of vocalization (±SEμ). I found that during this period unshocked subjects emitted very few sounds during that crossed the 47.1-dB threshold. Their mean level of vocalization was 47.4 dB (±0.28). By contrast, subjects that received weak shock vocalized at a level of 62.6 dB (±2.44). Finally, subjects that received intense shock vocalized at a level of 87.5 dB (±0.58). An analysis of variance showed that shock treatment had a significant impact, F(2, 21) = 191.52, p < .001. A post hoc Newman-Keuls test revealed that the differences between each of the groups were significant.

The mean levels of straining (±SEμ) observed during the first 0.75 s of the shock period were 0.06 N (±0.06), 1.24 N (±0.20), and 8.91 N (±0.33) for the unshocked, weak shock, and intense shock groups, respectively. An analysis of variance revealed that shock treatment had a significant impact, F(2, 21) = 457.84, p < .001. A post hoc comparisons with the Newman-Keuls test showed that differences between each of the groups were significant.

The mean levels of pain reactivity (±SEμ) exhibited during baseline testing were 5.19 s (±0.21), 5.14 s (±0.24), and 5.13 s (±0.18) for the unshocked, weak shock, and intense shock groups, respectively. These differences did not approach statistical significance, F(2, 21) = 0.3, p > .05.

The mean levels of pain reactivity observed after shock treatment are depicted in Figure 3. It is obvious that rats that experienced the intense shock became hypalgesic. However, the weak shock appears to have had only a transient impact on pain reactivity. These impressions were confirmed by analysis of variance. This analysis showed that shock treatment had significant impact on pain reactivity, F(2, 21) = 7.47, p < .05. The trials effect, F(4, 84) = 1.77, p > .05, and the interaction of trials with shock treatment, F(8, 84) = .99, p > .05, did not approach significance. A post hoc Newman-Keuls test (p < .05) was used to compare the overall group means. This test showed that animals in the intense-shock group were analgesic relative to subjects in the weak shock and unshocked groups. No other differences were significant.

Discussion

The results of the present experiment were anticipated by my working memory hypothesis. According to this hypothesis, the magnitude of hypalgesia observed is a function of the hedonic value of the stimulus representation. Because the hedonic value of the representation of a 0.1-mA shock is presumably much less than the hedonic value of a 1.0-mA shock, my account anticipated that weak shock would induce hypalgesia that is only a fraction of the hypalgesia elicited by the intense shock. The results confirmed this prediction.

The findings from this experiment pose further difficulties for the coulometric hypothesis. According to this hypothesis, the intense shock and weak shock schedules should have yielded equivalent reductions of pain reactivity because they have equivalent coulometric products. However, only the intense shock produced a significant hypalgesia. An advocate of the hypothesis might argue that the weak shock did not induce a significant hypalgesia simply because it was not aversive. However, this argument does not seem tenable because the rats vocalized and strained during the weak shock. This suggests the weak shock was indeed aversive. Still others might argue that even though the weak shock was aversive, it was below the range where the coulometric hypothesis holds. However, this seems unlikely because Church et al. (1967) provided evidence that a coulometric relation accurately describes the severity of very weak shocks (between 0.05 mA and 0.25 mA). One might still argue that it is difficult to compare the shock levels in the two studies because Church et al. administered their shocks through a grid floor rather than through fixed electrodes. However, even with this difference it still seems unlikely that my 0.10-mA shocks were less aversive than the 0.05-mA grid shock used by Church et al. In fact, one might argue that the shocks employed here were quite a bit more severe than those used by Church et
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al. There are two reasons for this. First, my use of fixed electrodes, combined with electrode paste, ensured constant low-resistance contacts. Secondly, I administered my weak shocks for 7.5 s, whereas Church limited shock duration to just 2 s. These considerations raise another concern, namely, that the coulometric relation does not hold for intense (1.0 mA) or prolonged (7.5 s) shocks. However, this explanation does not seem tenable because Fanselow (1984) and Terman et al. (1984) have provided evidence that the coulometric relation holds for shocks which are much more intense (e.g., 1.5 mA–3.5 mA) and much longer (e.g., 30 s–300 s). Clearly, we were in a range where the coulometric relation should have accurately described shock severity, but yet it failed to predict the magnitude of hypoalgesia. These findings suggest, at the least, that the use of the coulometric relation to predict hypoalgesia needs to be constrained. I will return to this issue in the General Discussion.

Rejecting the coulometric hypothesis poses difficulties for Fanselow’s extension of PDR theory. Recall that according to PDR theory, conditioned fear mediates the activation of the analgesic systems. Fanselow bolstered this theory by assuming that whether conditioned fear elicits an opioid or nonopioid hypoalgesia depends on the severity of the aversive event, which is determined by a coulometric relation. In terms of this extension of PDR theory, equivalent coulometric products should yield equivalent hypoalgesia because they should yield equivalent levels of conditioned fear. Contrary to this prediction, the present experiment clearly shows that equal products do not yield equal hypoalgesia. This finding might mean that equal levels of fear do not necessarily produce equal levels of hypoalgesia. Such an outcome would pose problems for PDR theory. Alternatively, the experiment may have failed because the coulometric relation does not accurately predict the degree to which a shock will establish a state of conditioned fear. If this were the case, one could maintain PDR theory but would be forced to reject Fanselow’s extension of the theory.

I recently completed an experiment that suggests the problem lies in using the coulometric relation to predict the degree to which a shock will establish a state of fear. In this experiment I exposed rats to shocks of the same duration and intensity as the shocks used in the present experiments. However, the shocks were administered through a grid floor in a 30 × 24 × 26-cm chamber. This allowed me to determine the degree to which each of the shock schedules induced freezing behavior. Freezing behavior was recorded (as described in Grau, 1984) for 10 min following each of the shock schedules. According to Bolles and Fanselow (Bolles & Fanselow, 1980; Fanselow & Bolles, 1979), freezing provides an sensitive index of fear. I found that unshocked subjects exhibited little freezing during the observation period (3.75%). Animals that received three weak shocks (0.1 mA, 7.5 s) froze 35.42% of the time. By contrast, animals that received three intense shocks (1.0-mA, 0.75 s) froze much more, 72.92% of the time. An analysis of variance confirmed that shock treatment had a significant impact, P(2, 9) = 13.94, p < .005, and a post hoc Newman-Keuls test showed that the three groups were significantly different from each other. The fact that the weak and intense shock schedules failed to induce an equal level of freezing suggests that coulometric relation does not accurately predict the degree to which a shock will establish a state of fear. This finding, in conjunction with the results of Experiment 2, suggests that we can maintain PDR theory but must reject Fanselow’s extension of it.

Unfortunately, rejecting Fanselow’s version of the coulometric hypothesis substantially weakens PDR theory, because this hypothesis allowed PDR theory to predict whether a state of fear will elicit an opioid or nonopioid hypoalgesia. In order to maintain the viability of PDR theory, this issue will have to be addressed. One potential solution would involve maintaining the assumption that shock severity determines whether a state of fear will elicit an opioid or nonopioid analgesia. However, such an account would require defining shock severity in some way other than by a coulometric relation. Alternatively, the assumption that shock severity predicts the form of analgesia could be rejected. One might then argue instead that the memory state of an aversive representation determines whether fear will produce an opioid or nonopioid hypoalgesia. Obviously, such an account would be very similar to our own working memory hypothesis. The only difference is whether a "fear mechanism" intervenes between the representation of an aversive event and the analgesic systems. Because it is unclear whether positing such a fear system adds in any way to our ability to predict the magnitude and form of analgesia, it appears more parsimonious simply to assume that the representation of an aversive event can directly activate the analgesic systems.

Experiment 3

The coulometric hypothesis proposed by Terman et al. (1984) assumes that the analgesic systems are activated by incoming nociceptive information. This perspective suggests that the time course of any subsequent hypoalgesia simply reflects the physiological and biochemical properties of the systems that mediate the reduction of pain reactivity. For example, consider how Terman et al. would account for the time course of the opioid hypoalgesia observed after a 30-s, 2.5-mA shock. In this situation, they would argue that an endogenous opiate was released during shock exposure and that the time course of the subsequent hypoalgesia simply reflects the decay of the opioid’s hypoalgesic action. This characterization of the analgesic systems suggests there may be some important inflexibilities in the way pain is modulated. In particular, it suggests that although the analgesic systems might be rapidly activated, recovery of pain reactivity may reflect a relatively slow passive decay process. Such a system, although simple, would have the disadvantage that it would not allow the organism to rapidly regain pain sensitivity in response to changes in its stimulus environment.

By contrast, my working memory hypothesis suggests that pain modulation might be a much more flexible process; it allows for both rapid decreases in pain reactivity and rapid recovery of pain sensitivity. The reason for this is that I assume the memory of an aversive event maintains the activation of the analgesic systems. In the absence of such an active memory of the aversive event, I assume that the analgesia will rapidly decay. Of course, I admit this decay will not be instantaneous, because the analgesic systems presumably have some resonance. However, I assume this resonance plays a relatively minor role in determining the decay of analgesia. This perspective suggests that an opioid hypoalgesia might be observed long after the termination of
shock because the memory of the aversive event maintains the release of the opioid, and not because the opioid has a long-lasting hypoalgesic action. This characterization actually fits well with the known hypoalgesic quality of some opioids. For example, although enkephalins can produce a strong hypoalgesia, this hypoalgesia decays quite rapidly (Belluzzi et al., 1976).

My claim that the memory of an aversive event maintains the activation of the analgesic systems makes a novel prediction: It suggests that variables which speed the decay of the memory should also speed the decay of hypoalgesia. I recently obtained some evidence for this claim. My test of the hypothesis relied on the common assumption that working memory has a limited capacity (e.g., Atkinson & Shiffrin, 1968; Wagner, 1981). Because of this limited capacity, salient stimuli can displace old representations from working memory (Peterson & Peterson, 1959; Wagner, 1981). This suggests that one should be able to displace the representation of an aversive event by presenting a salient “distractor” stimulus. If the representation of the aversive event in working memory maintains the activation of the analgesic systems, then this manipulation should speed the decay of hypoalgesia. Supporting this, I have recently shown that presenting a distracting stimulus—a flashing light—after shock attenuates both the nonopioid and opioid forms of hypoalgesia (Grau, 1986, 1987).

The present experiment extends this distractor effect in a novel way. I attempt to show that following an intense shock with a weak shock “distractor” attenuates the subsequent hypoalgesia. The basic idea behind this experiment is that the weak shock distractor will displace the representation of intense shock from working memory and replace it with one for weak shock. According to my hypothesis, the magnitude of hypoalgesia observed after an aversive event depends upon the hedonic value of the memory for the event. Thus, decreasing the hedonic value of the memory should attenuate hypoalgesia. In terms of SOP, I am assuming that there are stimulus properties that distinguish a weak shock from an intense shock. If so, then presenting the weak shock should activate the elements that encode its unique properties to working memory, which, in turn, should act to displace the elements that encode the hedonic value of the intense shock from working memory. Again, according to my application of SOP, displacing the elements that encode the hedonic value of the intense shock from working memory should attenuate hypoalgesia.

An important consideration in the design of the present experiment is the choice of the shock parameters. First, the intense shock must be set at a level that induces a strong hypoalgesia. Secondly, the weak shock should be set at a level that is noticed but that has negligible algesic impact. Both of these requirements can be met by employing the shock parameters used in Experiment 2. In that experiment and elsewhere (Grau, 1984, 1987), I found that three intense (1.0-mA, 0.75-s) shocks elicit a strong and long-lasting hypoalgesia. I also showed that three weak (0.1-mA, 7.5-s) shocks have a negligible impact on pain reactivity. Importantly, I provided evidence that the weak shocks were noticed because they induced vocalization and struggling.

The design of the present experiment involved four groups of rats. One group (intense—nothing) received intense shock and nothing after the shock. Another group (intense—weak) received a weak shock immediately after each intense shock. A third group (nothing—weak) received nothing during the intense shock periods, but did receive the weak shocks. The final group (nothing—nothing) served as our unshocked controls.

Method

Subjects. The subjects were 24 rats of the same age, sex, and strain as used in Experiment 1.

Apparatus. The apparatus was the same as the one used in Experiment 1.

Procedure. The rats were acclimated and tested for baseline pain reactivity as described in Experiment 2. The subjects were then randomly assigned to four groups. Group intense—nothing received three intense, 1.0-mA, 0.75-s shocks spaced 20 s apart. Subjects in Group intense—weak experienced a weak, 0.1-mA, 7.5-s shock after each of the intense shocks. Group nothing—weak experienced the three weak, 0.1-mA, 7.5-s shocks spaced 12.5-s apart. Finally, subjects in Group nothing—nothing served as our unshocked controls. After the last shock, or an equivalent period of restraint, pain reactivity was tested as described in Experiment 1.

Results

I found that the intense shock alone elicited a strong hypoalgesia. Presenting a weak shock immediately after each of the intense shocks attenuated this hypoalgesia.

Analysis of the baseline tail-flick latencies revealed that the groups did not differ prior to shock treatment. The mean baseline values (±SE) were 4.92 s (±0.18), 4.89 s (±0.25), 5.08 s (±0.19), and 5.06 s (±0.20) for the intense—nothing (IN), intense—weak (IW), nothing—nothing (NN), and nothing—weak (NW) groups, respectively. An analysis of variance showed that these differences did not approach significance, all F<sub>1, 20</sub> < 0.56, p > .05.

Figure 4 depicts the mean tail-flick latencies observed after shock. It is apparent that animals that experienced intense shock alone (Group IN) became hypoalgesic. By contrast, exposure to weak shock alone (Group NW) did not induce a strong hypoalgesia. Most important, subjects that experienced a weak shock immediately after each of the intense shocks (Group IW) displayed much less hypoalgesia than subjects that received just intense shock (Group IN).

These impressions were confirmed by an 2 x 2 (between-subjects) x 5 (within-subjects) analysis of variance. In this analysis, intense shock treatment (intense shock or nothing) was treated as one of the between-subjects variables, and weak shock treatment (weak shock or nothing) was treated as the other. The repeated tail-flick tests constituted the within-subjects term. This analysis revealed that intense shock treatment had a significant impact, F(1, 20) = 14.53, p < .005, on pain reactivity. Most important, the interaction term showed that the impact of intense shock on pain reactivity depended upon whether the subjects experienced weak shock, F(1, 20) = 4.59, p < .05. The analysis also revealed that weak shock treatment, per se, did not have a significant impact on pain reactivity, F(1, 20) = 1.10, p > .05. Post hoc comparisons of the group means with a Newman-Keuls test (p < .05) showed that the subjects that received only intense shock (Group IN) were significantly more hypoalgesic than the other three groups. No other group comparisons were significant.
The within-subjects terms revealed a significant trials effect, \( F(4, 80) = 21.53, p < .001 \). Importantly, the change in pain reactivity observed across trials depended upon weak shock treatment, \( F(4, 80) = 3.40, p < .05 \). The trials effect did not interact significantly with either intense shock treatment, \( F(4, 80) = 1.63, p > .05 \), or the combination of weak and intense shock treatments, \( F(4, 80) = .44, p > .05 \).

Discussion

I found that three intense shocks alone elicited a strong hypoalgesia. This finding replicates the results of Experiment 2 and other work (Grau, 1984, 1987). As in Experiment 2, the weak shock alone had a negligible impact on pain reactivity. Most important, I observed that the hypoalgesia elicited by intense shock could be attenuated by following each of the intense shocks with a weak shock distractor. This finding provides strong support for my working memory hypothesis.

The findings of this experiment appear to pose further difficulties for the coulometric hypothesis. First, this hypothesis anticipated that the weak and intense shock alone would elicit equivalent hypoalgesia, because their coulometric products are equal. However, as in Experiment 2, only the intense shock schedule induced a significant hypoalgesia. This observation is important because in Experiments 2 and 3 different aspects of the shock schedule were equated; in Experiment 2 the time between shocks was kept equivalent, whereas in Experiment 3 the interval between shock onsets was kept equivalent. Secondly, the coulometric hypothesis would not have anticipated that following an intense shock with weak shock would attenuate hypoalgesia. Rather, according to this hypothesis, presenting further exposure to shock should, if anything, have simply further activated the analgesic systems.

In this experiment I found that the weak shocks acted as an effective distractor. In terms of SOP, a stimulus will be a good distractor only if it is of sufficient duration and intensity to strongly activate its representation to working memory. This implies that three 7.5-s presentations of a 0.1-mA shock are sufficient to strongly activate its representation to working memory. This observation has implications for an assumption made in Experiment 1: I assumed that there were 20 s of a more intense shock (0.25 mA) was sufficient to nearly fully activate its representation to working memory. The results of the present experiment appear to corroborate this assumption.

General Discussion

From an empirical perspective these experiments are important because they demonstrate a number of novel findings. First, Experiment 1 showed that increasing the duration of an aversive event can actually decrease both the persistence of hypoalgesia and the magnitude of the nonopioid hypoalgesia. Secondly, Experiment 2 demonstrated that a long–weak shock activates the analgesic systems much less than does a brief–intense shock. This was observed even though the weak shock was clearly aversive and was presented for much longer period of time than the intense shock. Experiment 3 demonstrated that much less hypoalgesia is observed after a series of intense shocks, if each of the intense shocks is followed by a weak shock.

Theoretical Implications

The present experiments are also important from a theoretical perspective because they provide evidence for my working memory hypothesis, and evidence against the coulometric hypothesis. According to the coulometric hypothesis, the magnitude and form of hypoalgesia is determined by the product of Intensity × Duration. In addition, it is assumed that the product needed to activate the nonopioid system is much higher than the product needed to activate the opioid system. The coulometric hypothesis clearly predicts that increasing the duration of an aversive event that elicits a transient nonopioid hypoalgesia should augment the nonopioid hypoalgesia. In fact, in Experiment 1 the opposite was found. In Experiment 2 a basic claim of the coulometric hypothesis was tested, namely, that stimuli having the same coulometric product should yield equivalent hypoalgesia. Contrary to this basic supposition, I found that long–weak shocks produce negligible hypoalgesia compared with brief–intense shocks even though both shocks had the same coulometric product. The results of Experiment 3 pose further problems for the coulometric hypothesis because it did not anticipate that presenting a weak shock after an intense one would attenuate hypoalgesia. Rather, it predicted the opposite, that further nociceptive stimulation would further activate the analgesic systems.

The findings provide strong support for my working memory hypothesis. According to this hypothesis, the central representation of an aversive event in working memory activates the analgesic systems. It is further assumed that a nonopioid hypoalgesia will be observed when the representation is in the focal A1 state, and an opioid hypoalgesia will be observed when it is in the peripheral A2 state. This hypothesis anticipates that there will be net decay from the focal A1 to the peripheral A2 state if a stimulus is presented for longer than the period required to
nearly fully activate its representation. The immediate impact of this redistribution will be a decrease in the nonopioid hypalgesia and an increase in the opioid hypalgesia. In addition, the net decay from the A1 to the A2 state will facilitate the decay of hypalgesia upon shock termination. Experiment 1 demonstrated that increasing the duration of an aversive event can have each of these consequences. My hypothesis also readily accommodates the results of Experiment 2—long–weak shocks produce negligible hypalgesia compared with brief–intense shocks. This was anticipated because I assume the magnitude of hypalgesia is a simple function of the hedonic value of the memory of the aversive event; increasing the duration of a weak shock might facilitate the activation of its representation to working memory, but the hedonic value of its representation would still be a fraction of the hedonic value associated with intense shock. The last experiment provided support for a novel prediction of the working memory hypothesis, namely, that following intense shocks with weak shock will attenuate hypalgesia. I anticipated this outcome because the weak shock should displace the memory of intense shock and replace it with one for weak shock. Consistent with this prediction, Experiment 3 demonstrated that following intense shock with weak shock does indeed attenuate hypalgesia.

The Coulometric Hypothesis Revisited: Constraining Its Application

It is clear that in my experimental paradigm the working memory hypothesis provides a much more accurate account of the data than does the coulometric hypothesis. However, it must be acknowledged that the coulometric hypothesis appears to adequately describe the activation of the analgesic systems under other experimental conditions (e.g., Terman et al., 1984). The paradigm where the coulometric hypothesis does appear to hold (Terman et al., 1984) differs from the present one in a variety of ways. One important difference is that the subjects are removed from the shock apparatus in order to test pain reactivity. This procedure exposes animals to a variety of distracting stimuli. According to my theory, these stimuli should act to displace the representation of shock from working memory and, hence, undermine the degree to which the analgesic systems are activated by memorial processes (Grau, 1986, 1987). In addition, removing the animals from the shock chamber removes the animals from the cues associated with shock. Again, this should minimize the degree to which high-level psychological processes activate the analgesic systems (Fanselow, 1984; Grau, 1986, 1987).

Given that both theory and data suggest removing the animals from the shock chambers to test pain reactivity will attenuate the contribution of high-level psychological processes (Fanselow, 1984; Grau, 1986, 1987), one might expect that much more intense shocks would be needed to induce reductions of pain reactivity. Indeed, researchers (e.g., Terman et al., 1984; Watkins & Mayer, 1982) who remove their subjects from the shock apparatus in order to test pain reactivity typically employ shock parameters that are dramatically more severe than the shock parameters employed in the present experiment. For example, Terman et al. (1984) exposed rats to more than 30 s of 2.5-mA shock to obtain hypalgesia, whereas I employed just 2.25 s of 1-mA shock. This difference in shock severity represents a second important difference between the experimental paradigms where the coulometric hypothesis does and does not appear to hold.

A third important difference lies in the role of higher neural processes. Meagher and I (1987), as well as others (Terman et al., 1984; Watkins & Mayer, 1982), have shown that manipulations designed to disrupt forebrain functioning (decerebration and administration of high doses of pentobarbital) have little impact on the “analgesia” observed after severe and/or long shocks. This suggests that the analgesic systems in the brainstem can be directly activated by incoming nociceptive information. However, we have shown that this direct mode activation is employed only when an organism is exposed to a severe (e.g., 75 s of 1.0-mA shock) aversive stimulus; decerebration and administration of pentobarbital do prevent relatively mild (2.25-s, 1.0-mA) shock from inducing a significant change in pain reactivity (Grau, 1987; Meagher & Grau, 1987). This suggests that forebrain systems mediate the activation of the analgesic systems in response to mild aversive stimuli.

In summary, the findings reviewed here suggest that the analgesic systems may be activated in two ways: directly by incoming nociceptive information or by higher neural/psychological processes. I have suggested that the hypalgesia observed in situations where the organism is exposed to severe shocks and then removed from the shock apparatus to be tested may reflect primarily the direct activation of the analgesic systems. The coulometric hypothesis may capture the conditions under which the analgesic systems are activated by this direct, “low-level mode” of activation. However, when mild shock is employed and care is taken not to disturb the subjects, the hypalgesia appears to reflect the influence of higher mechanisms. The results of the present set of experiments clearly show that the coulometric hypothesis does not accurately describe this “high-level mode” of activation (cf. Fanselow, 1984). Rather, the results suggest that my working memory hypothesis may correctly predict the conditions under which high-level processes activate the analgesic systems.

Obviously, a complete account of the variables that control the activation of the analgesic systems will need to address both the high- and the low-level modes of activation. However, I would like to suggest that the high-level mode of interaction may be of more general interest. There are two reasons for this. First, the high-level mode of activation may be much more frequently employed because organisms presumably encounter mild aversive stimuli more frequently than they encounter severe aversive stimuli. Secondly, both theory and data suggest that higher neural processes mediate the activation of the analgesic systems in response to the expectation of an aversive event (e.g., Bolles & Fanselow, 1980; Fanselow, 1982, 1984; Grau, 1987; Ross & Randich, 1985; Watkins & Mayer, 1982). These considerations suggest that the high-level mode of activation may be frequently employed to dynamically modulate pain reactivity. By contrast, the low-level mode of activation may serve as a “back-up” that is used only under the most extreme conditions. Further work is needed to evaluate these conjectures. In particular, researchers need to delineate (a) the conditions under which the high- and low-level modes of activation are employed; (b) the rules that describe whether a given mode will
elicit an opioid or nonopioid hypoalgesia; (c) the impact of activating the opioid and nonopioid hypoalgesic systems on the experience of pain; and (d) the physiological and biochemical systems that mediate analgesia.

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