Classical conditioning and pain: Conditioned analgesia and hyperalgesia

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ABSTRACT

This article reviews situations in which stimuli produce an increase or a decrease in nociceptive responses through basic associative processes and provides an associative account of such changes. Specifically, the literature suggests that cues associated with stress can produce conditioned analgesia or conditioned hyperalgesia, depending on the properties of the conditioned stimulus (e.g., contextual cues and audiovisual cues vs. gustatory and olfactory cues, respectively) and the proprieties of the unconditioned stimulus (e.g., appetitive, aversive, or analgesic, respectively). When such cues are associated with reducers of exogenous pain (e.g., opiates), they typically increase sensitivity to pain. Overall, the evidence concerning conditioned stress-induced analgesia, conditioned hyperalagesia, conditioned tolerance to morphine, and conditioned reduction of morphine analgesia suggests that selective associations between stimuli underlie changes in pain sensitivity.
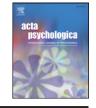
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Contents

1. Introduction

Pavlov (1927) observed that pairing an initially innocuous stimulus (i.e., conditioned stimulus, CS) with a biologically relevant stimulus (i.e., unconditioned stimulus, US) caused subsequent presentations of the CS to elicit a conditioned response (CR) that is usually similar to the unconditioned response (UR) evoked by the biologically relevant stimulus. This associative process is widely known as classical or Pavlovian conditioning, and it is thought to play an important role in the modulation of pain sensitivity (e.g., Flor, 2000). Our operational definition of pain sensitivity includes diverse dependent variables utilized in experiments using humans and animals to assess how Pavlovian conditioning changes sensitivity to painful stimulation (the various measures used to assess pain are summarized in Table 1). Although most definitions of pain incorporate a subjective aspect, our working

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Table 1
Measures of pain sensitivity.

Test	Subject	Method	Pain-related response
Tail-flick	Rodents	A heat source (typically produced by a light) is applied to the tail	*Latency to flick the tail
Hot plate	Rodents	Subjects are placed in a plate heated typically around 50 C	*Latency to: lick a paw, lick the hind paw, lift a paw
Formalin	Rodents	A subcutaneous injection of formalin (typically at 15%) is administered to the dorsal surface of a hind paw	*Latency to: lick a paw, lick the hind paw, lift a paw
Analgesiometer	Rodents	Constant increase of pressure applied to a paw	Amount of pressure before withdraw of the paw, *latency to withdraw the paw
Flinch/Jump	Rodents	A series of 10 ascending followed by 10 descending shocks are provided by means of a grid floor	The magnitude of rodents flinch/jump to shocks is measured on a continuous scale
Pain threshold/Pain tolerance	Humans	Electrodes provide ascending series of electric shocks. Similar to the method of limits used in psychophysics	Level of shock at which subjects report pain perception (pain threshold) or unbearable pain (pain tolerance)

Note: *Latency refers to the first observation of behavior after onset of pain-inducing stimuli.

definition of pain here refers to objective nociceptive responses, which allows the incorporation of diverse experimental preparations and species into the discussion. Here we review experimental evidence involving classical conditioning preparations that produce a change in pain sensitivity. Importantly, the direction of change in pain sensitivity seems to be modulated by the types of stimuli entering into associations. Several theoretical frameworks have been purposed within the associative literature to account for selective associations between stimuli. As others have previously proposed (e.g., Domjan & Galef, 1983; Garcia & Koelling, 1966; Lolordo & Droungas, 1989; Seligman, 1970, 1971), here we assume that both readiness of stimuli to enter into association and the form of resultant conditioned responses arise from evolutionarily-selected biases. More specifically, the selectivity of associations plays a role in determining whether analgesia or hyperalgesia will be observed in response to CSs paired with specific USs. Surely there are neurophysiological mechanisms underlying each of the phenomena described here; however, this review is focused at the psychological level of analysis.

We start our review by addressing the unconditioned analgesic properties of stressful stimulation and the conditioned stress-induced analgesia effect. We then discuss conditioning preparations that affect pain sensitivity through associations with exogenous opiates (e.g., morphine injections). In this assessment we distinguish circumstances that lead to analgesia and hyperalgesia. Specifically, we review the central phenomena of stress-induced analgesia and how preparations that differ in the types of CSs used can produce hyperalgesia instead. Additionally, we discuss the basic phenomena of morphine tolerance, focusing on how the nature of the stimuli used influences the direction of the change in sensitivity to pain.

2. Unconditioned response to stress: analgesia

A number of circumstances seem to selectively modulate responses to painful stimuli (Melzack & Wall, 1965). For example, soldiers severely wounded in the battlefield seldom complain immediately after being injured (e.g., Beecher, 1959), and marathon runners show little pain after being injured during a race (e.g., Hoffman, Lee, Zhao, & Tsodikov, 2007; Koltyn, 2000). These anecdotal examples and field reports are concordant with controlled laboratory observations in which stress induced by administering noxious stimuli, intense physical activity, etc. produce a decrease in pain sensitivity. In laboratory situations, rats that have been stressed by centrifugal rotation exhibit a higher threshold for pain in the tail-flick test (see Table 1) administrated soon after rotation than do control rats. Moreover, pain sensitivity is negatively correlated with the overall time that the animal spent in the centrifuge apparatus (Green & Lee, 1987). Similarly, several studies have reported that electric shocks temporarily reduce pain sensitivity in animals subsequently tested with tail-flick (e.g., Hayes, Bennett, Newlon, & Mayer, 1978) and hot-plate tests (e.g., Hayes et al., 1978; Ross & Randich,

1984; for a description of the tests, see Table 1). Even the stress of mere exposure to novel situations produces a temporary decrease in pain sensitivity in animals, as assessed by measurement of pain-related responses (e.g., Bardo & Hughes, 1979; Foo & Westbrook, 1991; Rochford & Dawes, 1993; Sherman, 1979). Thus, anecdotal and experimentally controlled evidence have begun to identify specific situations in which an unconditioned analgesic response will be observed (cf. Meagher et al., 2001).

The unconditioned response of a temporary decrease in pain sensitivity to stressors and noxious stimuli plays a role in pain modulation in humans as well as nonhuman animals. For example, analgesic effects have been observed immediately following intense physical activity (Droste, Greenlee, Schreck, & Roskamm, 1991) such as long distance running (Janal, Colt, Clark, & Glusman, 1984) and swimming (Scott & Gijbers, 1981). Physical stressors such as loud noises (Rhudy & Meagher, 2001), thermal stimulation (Rhudy, Grimes, & Meagher, 2004), and footshocks (Willer, Dehen, & Cambier, 1981; Willer & Ernst, 1986) have also been shown to produce analgesic effects in humans. In addition to physical stressors, stress induced by having participants solve mental arithmetic problems (Bandura, O'Leary, Taylor, Gauthier, & Gossard, 1988) and by administrating challenging memory tests (Frid & Singer, 1979; Frid, Singer, Oei, & Rana, 1981) also produce a temporary decrease in reported pain. Moreover, Melzack (1975) demonstrated that mild electric shocks reduce perceived severity of diverse pain syndromes in clinical populations for a relatively long duration (i.e., up to several hours and occasionally lasting for days or even weeks).

3. Conditioned stress-induced analgesia

The demonstration that stressful situations can produce an unconditioned reduction in the severity of pain sensitivity led Chance, White, Krynock, and Rosecrans (1977) to assess the possibility that an initially neutral stimulus, through pairings with a stressor, might also come to produce a reduction in the response to painful stimulation. In their experiment, on each of seven training days rats in the Unshocked Control group were merely placed in an operant chamber, while rats in the Conditioning group received a 15-s footshock in the operant chamber. On Day 8, all subjects were assessed for pain sensitivity with the tail-flick test in the operant chamber. The Conditioning group exhibited less pain sensitivity than the animals in the Unshocked Control group. Chance et al. concluded that the suppression of pain observed in the Conditioning group was due to Pavlovian associations. In their experiment, the operant chamber presumably served as a CS (i.e., contextual conditioning), while the footshock acted as a US. Decreased pain sensitivity in the absence of the physical stressor (e.g., the footshock) at the time of testing was thought to be due to the conditioned analgesia elicited by the operant chamber, but no control group that received footshock in the absence of the operant chamber of testing was included. As mentioned previously, in this experiment the context

served as the CS, whereas in other experiments cited in this review the CS was usually a discrete cue. Although conditioning of contexts and discrete cues may depend on somewhat different neurobiological processes, behavioral control by the two is highly similar in almost all instances except those in which the contingencies between cues and context were experimentally manipulated to maximize differences. To our knowledge, the reports of Chance et al. (e.g., Chance et al., 1977; Rosecrans & Chance, 1976) were the first demonstrations of conditioned stress-induced analgesia (a.k.a. conditioned autoanalgesia [e.g., Rochford & Stewart, 1987], more generally known as conditioned analgesia [e.g., Ross & Randich, 1985]).

The early findings of conditioned stress-induced analgesia (e.g., Chance, 1979; Chance, White, Krynock, & Rosecrans, 1978, 1979; Chance et al., 1977; Rosecrans & Chance, 1976) together with evidence of the conditioning of endogenous opiate mechanisms (e.g., Fanselow, 1979; Fanselow & Bolles, 1979a,b) received immediate attention from animal learning researchers. However, it was not until 23 years later that Flor and Grüsser (1999; also see Flor, Birbaumer, Schulz, Grüsser, & Mucha, 2002) presented evidence of conditioned stress-induced analgesia in humans. They used three groups of undergraduate participants who experienced five days of training. The Experimental group and Control Group 1 received pairings of a green light (CS) and a mental arithmetic test accompanied by a loud white noise (conjointly the US) on each of these days. Control Group 2 received a similar treatment, but the CS was not presented. After training, participants were tested for pain threshold and pain tolerance (see Table 1). To control for any possible conditioned stress-induced analgesia due to the conditioning context, testing was conducted in a different room from that used during training. Testing occurred in the presence of the CS for the Experimental group and Control Group 2, and in the absence of the CS for Control Group 1. As expected, pain threshold and pain tolerance did not differ between the two control groups. However, subjects in the Experimental group reported higher pain tolerance and pain threshold levels relative to both control groups, thereby demonstrating conditioned analgesia. Note that the lack of differences between the two control groups refutes any interpretation based on of an unconditioned effect at test, which confounded some earlier reports (e.g., Chance et al., 1977).

Importantly, not all CSs paired with stressors readily produce conditioned stress-induced analgesia. Williams and Rhudy (2007) assessed pain threshold in humans that received pairings of emotionally charged facial expressions (e.g., happy faces or fearful faces, counterbalanced) with shock or the absence of shock in a conditional discrimination task. Interestingly, only fearful faces served as effective CSs for eliciting stress-induced analgesia. Happy faces paired with shock (and fearful faces not paired with shocks) did not produce such a response. It is possible that the fearful faces were not only CSs, but also weak USs, so that after conditioning they produced both conditioned and unconditioned fear that summated sufficiently to produce analgesia. These results suggest that conditioning is in part dependent on the nature of the CS (also see Domjan, 1983; Domjan & Galef, 1983; Garcia & Koelling, 1966; Lolordo & Droungas, 1989; Seligman, 1970, 1971).

4. The role of conditioning in conditioned stress-induced analgesia

The early reports of conditioned stress-induced analgesia (e.g., Rosecrans & Chance, 1976) claimed that the reduction in pain sensitivity observed in their experiment was due to conditioning. As previously mentioned, their design lacked several control conditions, which allowed explanations of the observed analgesic response in terms other than those of associations between a stimulus and a stressor. For instance, Chance et al. (1977) had only one control group, which received no shock. Therefore, it is possible that the reduction in pain sensitivity on their tail-flick test was due to an unconditioned effect produced by the shock rather than a conditioned analgesic response (i.e., the control group should have received unpaired US presentations instead of no US at all). In a subsequent experiment, Chance et al.

(1978) used a better control group in which all subjects were exposed to shocks, but in this study the handling, shock delivery, and stimulus differed between the experimental and control groups. Hayes et al. (1978) also reported conditioned stress-induced analgesia, but their conditioning groups received an injection of naloxone before the test, whereas the control group did not receive an equivalent injection. Consequently, the analgesia observed in Hayes et al. might have been due to an unconditioned effect of the stress induced by injection instead of a conditioned response. Acknowledging these considerations, Fanselow and Bolles (1979b) gave forward pairings of the CS (which consisted of a punctuate cue [e.g., a tone]) and the shock (US) to the experimental group and backward pairings (e.g., US–CS) to the control group. Note that moderate numbers of backward pairings are known to result in little or no conditioned responding. Testing was conducted in a context different from the one used for training; however, their dependent variable was freezing (a variable associated with fear) which is not a direct measure of pain sensitivity. In summary, we consider all of the early reports to be suggestive but not conclusive evidence of a conditioning mechanism underlying early reports of conditioned stress induced-analgesia.

MacLennan, Jackson, and Maier (1980) also recognized drawbacks of the previous studies and conducted two experiments to assess the role of conditioning in pain sensitivity as measured by the hot plate test (Experiment 1) and the tail-flick test (Experiment 2). In their Experimental conditions, rats were exposed to shocks in one of two contexts (counterbalanced), whereas rats in their Control conditions did not receive shock, but were equally exposed to the contexts. Half of the animals in the Experimental condition were tested in the context in which they received the shock, while the other half of the rats was tested in the context in which they never received shocks. Only the rats in the Experimental conditions that were tested in the shock context (CS) showed reduced pain sensitivity (CR) on both the tail-flick and the hot plate tests. Thus, MacLennan et al. confirmed the suggestion of prior experiments but with more appropriate control conditions. In light of these studies, it appears clear that conditioned analgesia can be elicited by environmental stimuli associated with the a stressor by means of classical conditioning.

Several reports have looked for parallels between traditional phenomena in classical conditioning and conditioning of stress-induced analgesia. Such parallels would lend support to the view that the same classical conditioning processes underlie conventional conditioning and conditioned analgesic responses. For example, conditioned stress-induced analgesia has been observed in a second-order conditioning paradigm, and it has been found to be subject to extinction, latent inhibition, blocking, and conditioned inhibition. Specifically, second-order conditioning (Pavlov, 1927; Rescorla, 1985) consists of repeatedly pairing a CS (Y, a first-order CS) with the US (i.e., Y–US), and pairing a different CS (X, a second-order CS) with the first-order CS (i.e., X–Y) on separate trials. Given this procedure, X elicits a conditioned response despite its never having been paired with the US. Ross (1986) paired a visual CS with a shock and gave interspersed presentations of an auditory CS followed by the visual CS. Presentations of the auditory CS resulted in a reduction in pain sensitivity on the hotplate test relative to a control group that received unpaired presentations of the visual cue with the shock, and relative to a second control group that received unpaired presentations of the visual and auditory CS.

Fanselow (1984) demonstrated that conditioning stress-induced analgesia in rats is subject to extinction. Extinction refers to the decrease in a conditioned response due to nonreinforced presentation of the CS following an acquisition phase (e.g., Pavlov, 1927). In Fanselow's design, the experimental chamber (CS) served as the site of three presentations of a footshock US. Then, half of the rats were exposed to the experimental chamber without shocks being administered (all animals were equated for handling). Finally, pain sensitivity was evaluated in the experimental context using the formalin test (see Table 1). The subjects that received extra exposure to the chamber (i.e., extinction treatment)

displayed shorter latency pain responses relative to subjects that did not receive context extinction. The short latency pain responses in the group that received extra exposure to the context suggests that conditioned stress-induced analgesia was at least partially extinguished. Extinction of conditioned stress-induced analgesia has also been observed with the context as the CS in the tail flick-test (Maier & Watkins, 1991; Matzel, Hallam, & Miller, 1988, Experiment 1; Watkins, Cobelli, & Mayer, 1982; Wiertelak, Watkins, & Maier, 1992) and in the hot plate test (Ross & Randich, 1985, Experiment 3).

A decrease in conditioned responding is also observed when a to-be-trained CS is presented repeatedly before conditioning relative to a novel CS, a phenomenon known as the *CS-preexposure effect* (a.k.a. *latent inhibition*; Lubow & Moore, 1959). Maier and Watkins (1991) preexposed rats to either the context in which the rats later received a tailshock (i.e., experimental group) or to a neutral context (i.e., control group) for 2 h. After 1, 5 (Experiment 1A), or 80 (Experiment 1B) presentations of the tailshock, the training context elicited less of a conditioned analgesic effect in the tail-flick test in the rats that had been preexposed to the conditioning context than in the rats that were preexposed to an irrelevant context. Maier and Watkins's data suggest that CS preexposure impairs the development of a conditioned stress-induced analgesia response.

If the mechanism underlying conditioned stress-induced analgesia serves to facilitate efficient defensive behavior to threats by decreasing pain sensitivity (e.g., Bolles & Fanselow, 1980), then it should also be adaptive for analgesia to be terminated if the situation no longer predicts a threat, as occurs in the case of extinction. Similarly, a decrease in pain sensitivity should not be as readily elicited by familiar cues that subjects learned were safe before they were paired with an aversive US. Moreover, a signal that predicts that an aversive event will not happen (i.e., a safety signal) would be expected to produce inhibition of analgesic effects. Using rats, Wiertelak et al. (1992, also see Watkins et al., 1998) provided evidence for *conditioned inhibition* of stress-induced analgesia. A conditioned inhibitor (CS−) signals that an otherwise expected outcome will not occur. Such a CS− is commonly produced when it has a negative correlation with the otherwise expected outcome. Wiertelak et al. gave backward presentations of a footshock US followed by a light CS−. Large numbers of backward pairings of a CS and a US have been used to produce responses indicative of conditioned inhibition in standard conditioning preparations (e.g., Cole & Miller, 1999; Moscovitch & LoLordo, 1968). When the CS− was presented in compound with a conditioned excitatory context, the compound presentations produced increased pain sensitivity in the tail-flick test relative to pain sensitivity in the absence of the CS− (i.e., the CS− inhibited the conditioned analgesic response in a summation test [e.g., Pavlov, 1927]). Similarly, Lysle and Fowler (1988) observed a reduction in conditioned stress-induced analgesia when an excitatory CS, US, or a compound of these stimuli was presented in the presence of the CS−. Furthermore, Wiertelak et al. (1992) evaluated inhibition of conditioned stress-induced analgesia with a retardation test (e.g., Rescorla, 1969). They observed that when the CS− and the US were trained in a forward fashion (i.e., CS before US) following backward conditioning treatment, conditioned stress-induced analgesia developed slower relative to a stimulus which did not receive prior inhibitory training. Inhibition of the conditioned stress-induced analgesia has been repeatedly replicated in rats (e.g., Watkins et al., 1998). In contrast, Flor et al. (2002) failed to observe conditioned inhibition of conditioned stress-induced analgesia in humans using a differential inhibition training procedure in which one CS was followed by a stressor (e.g., mental arithmetic plus white noise [US]) while a CS− was presented without being followed by the stressor. Differential training has been shown to produce conditioned inhibition in other preparations with different parameters (e.g., Urcelay & Miller, 2006); however, Flor et al. used relatively few trials, which is known to produce weak or no inhibitory learning (e.g., Stout, Escobar, & Miller, 2004).

Blocking, which is an important phenomenon in the historical development of associative theories, has been shown to attenuate conditioned stress-induced analgesia. *Blocking* (Kamin, 1968) refers to the impairment in a conditioned responding to a stimulus (X), which was reinforced in compound (i.e., XY–US) with a stimulus that was elementally reinforced (i.e., Y–US) in a prior phase. Ross (1985) counterbalanced an auditory CS and a visual CS to evaluate blocking of conditioned stress-induced analgesia. One stimulus was first presented elementally followed by a shock (Y–US), then the two stimuli were presented in compound followed by a shock (XY–US). On a hot plate test, less reduced pain sensitivity was observed when the blocked cue X was presented relative to subjects that did not receive the initial Y–US training. These data suggest that blocking, a signature associative phenomenon, can be produced in conditioned stress-induced analgesia. This report, together with demonstrations of extinction, CS preexposure, conditioned inhibition, and second-order conditioning support an associative account of conditioned stress-induced analgesia.

5. Interactions of conditioned stress-induced analgesia and morphine administration

One of the conditions for producing conditioned stress-induced analgesia is that the stressor not only needs to be presented, but needs to produce an unconditioned stress response (or at least the stressor must be perceived). Such a response or sensation can be blocked at training if morphine is administered just prior to the conditioning trials, a situation that also attenuates a CS-elicited analgesia at test (Rochford & Stewart, 1987). Moreover, the unconditioned analgesic effect of stressors usually summates with the analgesic effect of opiates if the opiates are given at test. For example, reduced pain sensitivity, beyond that due to a stressor alone, has been reported when stressors such as footshock (Lewis, Sherman, & Liebeskind, 1981), tailshock (Hyson, Ashcraft, Drugan, Grau, & Maier, 1982), electroconvulsive shock (Belenky & Holaday, 1981), forced swim (Baamonde, Hidalgo, & Andrés-Trelles, 1989), and restraint (Appelbaum & Holtzman, 1984) are accompanied by opiates.

Stimuli associated with stress through conditioning are also capable of enhancing the analgesic effect of morphine (Johnston & Westbrook, 2003; Przewłocka, Sumová, & Lasoń, 1990). For example, Sherman, Strub, and Lewis (1984) observed an additive effect of morphine and conditioned stress-induced analgesia produced by presentation of a CS. Sherman et al. gave nine conditioning sessions in which a context and a footshock were paired. At test, morphine was injected prior to placement of the rats on a hot plate. Rats that were shocked in the context showed lower pain sensitivity relative to a) control subjects that never were exposed to the shock or the context (Experiment 1), b) control subjects that were familiar with the context but that had not received shock (Experiment 1), and c) control subjects that were shocked in a different context from the one used during testing (Experiment 3).

As mentioned previously, conditioned stress-induced analgesia appears to be, at least in part, due to the release of endogenous opiates (e.g., Fanselow & Baackes, 1982; Flor et al., 2002; Lichtman & Fanselow, 1991; Matzel et al., 1988). Thus, the enhanced analgesia observed when cues associated with stressors are combined with the administration of morphine might result from an additive combination of the opiate effect from the conditioned response plus the opiate properties of morphine (Abrahamsen, Stock, Caldarone, & Rosellini, 1993; Sherman et al., 1984). However, Przewłocka et al. (1990) did not observe this type of enhancement of morphine-induced analgesia in rats injected with an specifc k[1] opiate agonist (U69,593). Therefore, it appears that the analgesic enhancement of opioids produced by a CS associated with stressors depends on the site of action and receptor selectivity of the specific exogenous opioid that is administered.

The enhancement of morphine analgesia by a CS associated with stress has been replicated on several occasions using diverse

experimental controls and assessing different associative factors. For example, Rosellini, Abrahamsen, Stock, and Caldarone (1994) exposed rats to 0, 20, 100, or 200 mild footshocks in the same context used for testing the enhancement of morphine-induced analgesia. Their results supported the conclusion that the enhancement does not require a large number of trials as suggested previously (Abrahamsen et al., 1993). Caldarone, Abrahamsen, Stock, Mongeluzi, and Rossellini (1997) using a mild footshock did not observe conditioned stress-induced analgesia (perhaps due to the tail-flick test not being very sensitive). Instead, an enhancement of morphine-induced analgesia was seen in the presence of the CSs. Stock et al. (2001) focused on sex differences in the enhancement of analgesia by a CS associated with shock and found that the enhancement in female rats depends on the specific point in the subject's estrus cycle. The literature regarding the enhancement of analgesic effects of morphine by conditioned stress-induced analgesia is relevant to the design of treatments intended to help patients cope with pain. However, despite the attention that enhancement of morphine analgesic effects by conditioned stress-induced analgesia has received, the finding has not yet been reported in either healthy humans or clinical patients.

6. Not all cues associated with stressors produce conditioned stress-induced analgesia or enhancement of morphine-induced analgesia

We have reviewed evidence suggesting that stressors in general produce stress-induced analgesia, that stimuli associated with them produce conditioned stress-induced analgesia, and that such CSs can increase the antinociceptive effect of opiates such as morphine. However, there are cases in which these findings do not apply. Under select circumstances, these CSs can produce an increase in pain sensitivity, or hyperalgesia, to aversive stimulation (e.g., Imbe, Iwai-Liao, & Senba, 2006; Sandkühler, 2009) or to another CS associated with a stressor (Davis & Hendersen, 1985). However, the literature suggests that the phenomenon of conditioned hyperalgesia is quite elusive (e.g., Illich, Salinas, & Grau, 1991; Matzel & Miller, 1989).

Using parameters similar to the standard experiments reviewed above concerning conditioned stress-induced analgesia, Davis and Hendersen (1985) reported an increase in behavior indicative of pain in response to a CS associated to a stressor. Specifically, they gave 15 pairings of an auditory CS and a brief footshock. At test, they observed a decrease in tail-flick latencies (i.e., hyperalgesia) in the group that received the CS relative to a group that did not receive any CS. However, Illich et al. (1991), using the same parameters as Davis and Hendersen, found the opposite result (i.e., conditioned analgesia). Behavior on a tail-flick test was indicative of a reduction in pain sensitivity. Seeking to identify the factors that might contribute to the elicitation of a hyperalgesic response, Matzel and Miller (1987) noted that experiments in which an increase in pain sensitivity was reported had used short duration CSs (e.g., Davis & Hendersen, 1985) in contrast to studies failing to see hyperalgesia. In three experiments designed to assess the role of CS duration, they did not find hyperalgesia. Moreover, they found that analgesia did not increase when longer CSs were used. Additionally, Matzel and Miller (1987, 1989) noticed that hyperalgesia was reported when the test was conducted immediately after the presentation of the CS. They hypothesized that the mechanism by which the endogenous opiates work might be slow acting, and the immediate response to a CS associated with a stressor might produce sensitization of pain. However, their data did not support this hypothesis, and furthermore, no evidence of hyperalgesia was found. Thus, the basis of this discrepancy on the literature has not been resolved.

The analgesic effect of a CS associated with stressor has also been sought when the stressor is an internal malaise, as in conditioned taste aversion preparations. In a conditioned taste aversion preparation (e.g., Garcia, Kimeldorf, & Koelling, 1955), the unconditioned stressor is illness, which can be produced by an injection of LiCl or radiation, and the CSs are flavors. If an aversion is conditioned to a flavor, subjects will consume less of that flavor (typically dissolved in water) relative to subjects that have not received the flavor-LiCl pairings or subjects that have received the pairings of these stimuli but are tested with a different flavor from that used during training. Jensen and Smith (1985) examined whether saccharin-flavored water associated with LiCl would produce conditioned stress-induced analgesia comparable to that typically observed when the CS is the experimental context and the US is footshock. They found a decrease in pain sensitivity as assessed in a tail-flick test in the group that received context-shock pairings, but not in the group that received flavor-LiCl pairings relative to their respective controls. These findings suggest that not all aversive conditioning preparations are able to produce conditioned stress-induced analgesia. It could be that some CSs, like flavors, are processed in a different fashion relative to exogenous cues such as external contexts, lights, and auditory cues. Alternatively, it could be that the stress produced by illness does not induce an unconditioned analgesic response. Note that the two elements, the flavor CS and internal malaise US, involved in conditioned taste aversion have been proposed to enter into associations with features that differ from other conditioning preparations (e.g., Garcia & Koelling, 1966; Garcia et al., 1955; Rozin & Kalat, 1971; for a recent review and discussion, see Freeman & Riley, 2009).

Wiertelak et al. (1994) evaluated whether internal malaise can produce unconditioned analgesia. Using two different substances (LiCl and lipolisaccharide) that produce internal malaise and are typically used in conditioned taste aversion paradigms, they found an *increase* in pain sensitivity with both the formalin and the tail-flick tests. That is, Wiertelak et al. found unconditioned hyperalgesia instead of the expected analgesia (cf., Yirmiya, Lieblich, Liebeskind, & Garcia, 1988). Furthermore, they found that consumption of saccharin (i.e., a flavor CS) before the test increased pain sensitivity similar to that observed when LiCl and lipolisaccharides were provided prior testing (i.e., conditioned hyperalgesia; cf., Miller, Frombach, Scherer, & Jagielo, 1997).

Johnston and Westbrook (2003) did not find unconditioned or conditioned hyperalgesia using LiCl or lipolisaccharides with the hot plate or tail-flick tests. However, in a condition in which subjects received an injection of morphine before the tests, the analgesic effect of morphine was reduced by internal malaise. That is, rats that received an injection of LiCl just prior to testing exhibited greater pain sensitivity relative to rats that received an injection of saline. Therefore, illness, produced here by an injection of LiCl or lipolisaccharides, yielded a reduction in the *unconditioned* morphine-induced analgesia. This reduction is opposite in direction to the enhancement in morphine-induced analgesia produced by stressors such as electric shock. Also, this reduction of analgesia occurred in the absence of hyperalgesia in subjects that received saline instead of morphine.

Johnston and Westbrook (2003) additionally demonstrated that the conditioned hyperalgesia produced by stimuli associated with internal malaise can also affect the analgesic properties of morphine. Rats that at test had received a flavor CS (e.g., saccharin) that had been previously paired with LiCl exhibited a reduced analgesic response to morphine, relative to both a group that received unpaired presentations and a group of naive rats. That is, a conditioned reduction in morphine-induced analgesia was produced.

In summary, it seems that not all stressors produce changes in pain sensitivity in the same direction. The evidence that flavor CSs associated with stress produced by internal malaise results in hyperalgesia (Wiertelak et al., 1994) and a reduction of morphine-induced analgesia (Johnston & Westbrook, 2003) supports a role for selective associations in the modulation of pain sensitivity.

7. Conditioned morphine-induced analgesia

Morphine, as an unconditioned stimulus, produces several different unconditioned responses. For instance, aversive properties of morphine are observed in conditioned taste aversion experiments in which

morphine seemingly produces an internal malaise (e.g., Cappell, LeBlanc, & Endrenyi, 1973). However, appetitive properties of morphine are observed in conditioned place preference experiments in which animals typically spend more time in a compartment associated with appetitive reinforcers (e.g., Rossi & Reid, 1976). It appears that, at least in some animals, a predisposition exists for associating audiovisual cues with the appetitive properties of morphine, whereas gustatory and olfactory cues are more readily associated with the aversive properties of the opiate. Besides the appetitively and aversively motivated responses that morphine seems to elicit, a third response, analgesia, is its signature outcome. Interestingly, the μ opiate receptors, which are related to the perception of pain, become more active in both conditioned taste aversion and conditioned place preference situations when morphine is used as the US (Mucha & Herz, 1985, 1986).

Miller, Kelly, Neisewander, McCoy, and Bardo (1990) provided the first demonstration of behavior suggesting conditioned morphine-induced analgesia. They trained rats pairing saccharin-flavored water (CS) with an injection of morphine (US) or saline. In the first of two tests, consumption of saccharin-flavored water was found to be lower in subjects that received the saccharine solution paired with morphine relative to saline control subjects. Thus, the first test suggested the occurrence of conditioned taste aversion after training with morphine as the US. Then subjects were placed on a hot plate to test pain sensitivity. Animals that received conditioning with morphine during training (seven days before the test) exhibited less pain sensitivity than subjects that received saline instead of morphine. Thus, the two tests suggested that the conditioned response to saccharin involved both adverse affect and analgesia. As the tests occurred seven days after completion of training, these observations were not likely due to unconditioned effects of morphine. In a second experiment, Miller et al. gave an opioid antagonist (i.e., naloxone) before a hot plate test, which yielded a reduction of the analgesic conditioned response. However, no difference was detected in saccharin consumption between animals that received conditioning after naloxone injection relative to animals that received conditioning after saline injection. The former result suggests that, as in the experiments of conditioned stress-induced analgesia, the analgesic conditioned response to a flavor paired with morphine was, at least in part, opioid mediated. Moreover, Bardo and Valone (1994) reported similar findings administering LiCl instead of saline to the control group. But in this latter case, the analgesic effect observed could have been an artifact of conditioned taste aversion-induced hyperalgesia (e.g., Wiertelak et al., 1994).

The conditioning of morphine-induced analgesia has been reported with olfactory cues as well as of gustatory cues as CSs. Randall, Kraemer, Valone, and Bardo (1993) exposed animals to two different odors (banana and orange, counterbalanced) followed either by morphine or saline on separate conditioning trials. Subjects were then tested for pain sensitivity with each odor separately on consecutive days with the hot plate. This differential training procedure yielded conditioned morphine-induced analgesia only on the first day of testing. No differences were observed between the two odors on the second day of testing, which is problematic because the conditioned analgesic response should not have extinguished so quickly between the two test trials. In principle, the first test could have produced strong extinction of the conditioned analgesic response. However, a general decrease in pain sensitivity was observed on the second test, which would not be expected if extinction had occurred. Therefore, it is possible that the second test was influenced by conditioned stress-induced analgesia acquired on the first hot plate test, in which the test context was the CS and the aversiveness of the hot plate was the US. Similar findings supporting conditioned morphine-induced analgesia using an odor as a cue were obtained in an experiment that used a single odor CS and an unpaired control condition (Valone, Randall, Kraemer, & Bardo, 1998).

Although the results of Bardo and Valone (1994) and Miller et al. (1990) have been interpreted as evidence for conditioned morphine-induced analgesia, an alternative nonassociative explanation also can account for the data in those two reports. Bevins, Valone, Bradley, and Bardo (1995) noticed that the methods used in these reports all included habituation to the inactive hot plate (i.e., the hot plate being at 22 °C) after an injection of morphine. Thus, morphine might have prevented habituation to the hot plate, and consequently, these subjects at test might have experienced a novel situation. As mentioned previously, novelty seems to produce stress that induces unconditioned analgesia (e.g., Foo & Westbrook, 1991; Sherman, 1979), and the use of a novel hot plate has been seen to produce an analgesic effect relative to a familiar hot plate (e.g., Bardo & Hughes, 1979; Rochford & Dawes, 1993; Rochford, Dawes, & Stewart, 1993). Although Bevins et al. provided evidence supporting the role of novelty in inducing analgesia using procedures similar to those of the previous studies (Bardo & Valone, 1994; Miller et al., 1990), no evidence of novelty-induced analgesia was observed when Valone et al. (1998) used a higher dose of morphine. Valone et al. (1998) gave rats morphine (0, 3, 10 or 30 mg/kg) paired with an olfactory cue prior to exposure to the unheated hot plate during training. At test with the odor, they only observed an analgesic response in the 10 mg/kg condition. If the analgesic response was due to the novelty of the hot plate (because of impairment of habituation due to morphine effects during habituation treatment), then one would also expect novelty-induced analgesia when a higher dose was used (i.e., the 30 mg/kg condition). But, the lack of analgesia in the 30 mg/kg condition is not problematic for the conditioning account. Several reports suggest that the conditioned response to a US is an inverted U-shaped function of US intensity (Davis & Astrachan, 1978; Witnauer & Miller, 2013; but see, Annau & Kamin, 1961; Morris & Bouton, 2006), a prediction that is expected by some models of classical conditioning (e.g., Stout & Miller, 2007). This suggests that the conditioned analgesic effect would occur only with a moderate dose of morphine.

As mentioned before, morphine produces diverse unconditioned responses (e.g., appetitive, aversive, and analgesic). When flavor CSs are used, both the aversive and analgesic properties of morphine seem to become associated. This seems contradictory to the hyperalgesic response that a flavor produces when it is associated with other substances that cause an internal malaise, such as LiCl (e.g., Johnston & Westbrook, 2003; Wiertelak et al., 1994). Further investigation regarding morphine relative to LiCl as USs may elucidate why hyperalgesia is sometimes observed, whereas analgesia is observed in other situations.

8. Audiovisual and contextual cues, morphine, and conditioned tolerance

We previously reviewed data suggesting that diverse types of CSs (audiovisual cues such as lights, sounds, and contexts vs. flavors and odors) can differentially determine the response that is conditioned to them. When the US is a stressor (such as illness, shock, or heavy physical activity), audiovisual cues seem to produce a conditioned analgesic response (e.g., Flor et al., 2002; Rosecrans & Chance, 1976), but flavors seem to produce a conditioned hyperalgesic reaction (e.g., Johnston & Westbrook, 2003; Wiertelak et al., 1994). This inversion in the nature of the conditioned response is also observed when the US is an injection of opiates. In the previous section, we reviewed the conditioned analgesic effect of flavors and odors when they have been paired with morphine. Here, we will focus on the effects of pairing morphine with audiovisual cues.

Tolerance to a drug refers to a decrease in the effect that the drug produces when the dose is constant over repeated administrations, or to the necessity of increasing a drug dose to match initial levels of the drug effect. Several reports suggest that drug tolerance is, at least in part, an associative phenomena (e.g., McDonald & Siegel, 2004; Siegel, 2005; Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000; Spragg, 1940) that summates with nonassociative factors (e.g., Tiffany, Drobes, & Cepeda-Benito, 1992; Tiffany & Maude-Griffin, 1988). Siegel (1975)

found that tolerance to the analgesic effect of morphine can be conditioned to audiovisual cues. He administered a daily dose of morphine to rats across three consecutive days. After morphine administration, some subjects were returned to their home cages, while other subjects were placed on an unheated hot plate environment 30 min after morphine injection. In a third condition, subjects were placed on a heated rather than in the unheated hot plate environment with an injection of morphine. One day after the last training trial, all subjects were tested on the now heated hot plate for an analgesia test 30 min after injection of a single dose of morphine. An additional group of rats received only saline during training with the unheated hot plate and was tested on the now heated hot plate. The results showed lower levels of analgesia in the groups that received morphine paired to both the unheated and heated hot plate relative to the group that after morphine injection was placed in their home cages. Furthermore, the response of the groups that received morphine with exposure to the hot plate (heated or unheated) during training did not differ from the group that only received saline during training and testing. That is, tolerance, expressed as high levels of pain sensitivity, was observed only with repeated exposure of the drug in the same context in which testing occurred. Tolerance was not observed for a group equated in morphine administration but not context exposure. Siegel attributed this difference in pain sensitivity to the presence of the same environmental cues at test as had been associated with the effects of morphine during training. These contextual cues worked as a CS at test, producing conditioned tolerance to the analgesic effect of morphine (i.e., no decrease in pain sensitivity).

Findings that supported Siegel's (1975) observations and conclusions concerning the role of conditioning in the development of analgesia to morphine were later reported using different species (e.g., Kavaliers & Hirst, 1983; Schnur & Martinez, 1989), as well as diverse controls and test conditions (Siegel, 1976; Siegel, Hinson, & Krank, 1978; Tiffany & Baker, 1981). For example, support was found using conditional discriminations with different contextual cues serving as CSs with two different tests (hot plate and analgesiometer [for test description, see Table 1]; Siegel, 1976), using an unpaired contextual cue/morphine injection control and subsequent hot plate test (Siegel et al., 1978), and using a flinch/jump assessment of analgesia (Tiffany & Baker, 1981; for test description, see Table 1).

The development of tolerance to morphine analgesia has also been observed when CSs are interoceptive contextual cues. For example, Siegel (1988) showed that when a barbiturate (pentobarbital) was injected before morphine, it acquired the properties of a CS able to produce a conditioned tolerance response. Tolerance to the analgesic effect of morphine was observed when rats received pentobarbital during both training and testing, relative to groups for which the test conditions did not match those of training. Moreover, the early onset effects of a morphine dose serves as a CS for a future higher dose on the same trial. That is, a low dose of morphine paired with a later high dose was able to produce conditioned tolerance to the analgesic effects of the high dose (McDonald & Siegel, 2004). Magnetic fields have been used effectively as CSs, producing conditioned tolerance to morphine in mice (Kavaliers & Ossenkopp, 1985).

The contribution of associative processes to the development of opioid tolerance has also been supported by experiments that reproduce several fundamental conditioning phenomena. For example, extinction of tolerance to morphine analgesia has been reported when cues previously paired with the injection of morphine are presented repeatedly, each followed by an injection of saline in a second phase of training (e.g., MacRae & Siegel, 1987; Siegel, 1975; Siegel, Hinson, & Krank, 1979; Siegel, Sherman, & Mitchell, 1980). Additionally, the recovery of the conditioned response when a retention interval is imposed between extinction and testing, known as *spontaneous recovery* (e.g., Pavlov, 1927; Sissons & Miller, 2009), has been reported for extinction of conditioned tolerance to the analgesic effect of morphine (Millin & Riccio, 2002). Reduction of conditioned tolerance has also been

reported when a partial reinforcement schedule is used during training (e.g., Siegel, 1977). Reduced conditioned responding due to contingency degradation refers to the addition of nonreinforced CSs or nonsignaled US presentations interspersed among the CS–US pairings, an arrangement which usually produces lower conditioned responding relative to continuous reinforcement (e.g., Fitzgerald, 1963; Miguez, Witnauer, & Miller, 2012). Reduced conditioned tolerance of morphine-induced analgesia resulting from partial reinforcement has been observed when nonreinforced CSs have been added (Krank, Hinson, & Siegel, 1984; Siegel, 1977), but not when unsignaled USs were presented during training (Cepeda-Benito & Tiffany, 1996). Presumably, unsignaled USs that were presented on a fixed schedule of 6 h prior to each training trial in this last study could have served as an interoceptive CS, which may have resulted in a conditioned tolerance response to morphine.

A decrement in tolerance has also been produced by CS preexposure before the training phase (i.e., latent inhibition treatment), in which the environmental cues (including the injection procedure) were paired repeatedly with saline before they were paired with morphine (Siegel, 1977). Further experiments have shown that tolerance to the analgesic effect of morphine is also subject to blocking (Dafters, Hetherington, & McCartney, 1983) and overshadowing (Walter & Riccio, 1983), the better known forms of competition between CSs.

Conditioned tolerance to morphine is also observed in sensory preconditioning. *Sensory preconditioning* consists of a two-phase procedure. In the first phase, two neutral stimuli (i.e., stimuli that do not produce the response under study) are paired (e.g., X–A). In a subsequent phase, one of the stimuli is paired with the US (e.g., A–US). At test, the stimulus that did not receive training (X) is tested, yielding a conditioned response as if the US was expected even though X was never paired directly with the US (Brodgen, 1939). Dafters et al. (1983) gave tone-light pairings to rats during a first phase. In a second phase, they gave training for producing associative tolerance to morphine analgesia using the light as a CS. At test, the tone elicited conditioned tolerance to analgesia, providing further support for an associative contribution to tolerance of morphine. Additionally, noncontingent administration of glucose after each CS-morphine pairing enhances the associative development of tolerance to morphine analgesia (Siegel, 1999b), an effect that has been observed in other classical conditioning preparations (e.g., Matsumura et al., 2010; White & Messier, 1988). The observations of blocking, overshadowing, extinction, spontaneous recovery, partial reinforcement, sensory preconditioning, and glucose enhancement of the conditioned tolerance to the analgesic response of morphine all support the view of an associative contribution to tolerance. However, these demonstrations only address tangentially the nature of the specific conditioned response that leads to the observation of tolerance to effects of opiates.

It has been suggested that tolerance is produced in part by a compensatory conditioned response to the effects of the drug (for review of drug tolerance, see Siegel, 1999a, 2005; Siegel & Allan, 1998; Siegel et al., 2000; for a proposed locus and mechanism of action for associative morphine tolerance, see Mitchel, Basbau, & Fields, 2000). In the case of tolerance to morphine analgesia, such a compensatory response implies a hyperalgesic effect that attenuates the analgesic effect of morphine. The current perspective on drug tolerance (e.g., Siegel, 1999a) is that drugs, for example morphine, generate a change in the homeostatic state of organisms which is the effective US. Such deviations from homeostasis produce an unconditioned compensatory response (UR). If this UR is paired with contextual cues, then these cues can later serve as effective CSs for eliciting a conditioned compensatory response. If this is the case, then one should observe a hyperalgesic conditioned response when cues associated to morphine are presented in the absence of morphine analgesic effects at test. Siegel (1975) tested such CSs (paired with morphine injection during training) in the absence of an injection of morphine at test. Rats were equated for morphine experience during training. However, only one group received presentations of the CSs at test. This group

exhibited higher pain sensitivity (i.e., hyperalgesia) than a group for which the contextual cues differed between testing and training. Although conditioned hyperalgesia as a result of CS-morphine pairings has not always been found in situations that produce tolerance (e.g., Cepeda-Benito, Tiffany, & Cox, 1999), numerous experiments have found the hyperalgesic effect produced by contextual CSs associated with morphine using diverse preparations and controls. Among the associative phenomena observed here are the effects of a small early dose as a drug-onset CS (Sokolowska, Siegel, & Kim, 2002) and un-paired presentations of cues and morphine (Krank, Hinson, & Siegel, 1981). Moreover, conditioned hyperalgesia has been obtained with a within-subjects design (Siegel, 1975).

9. Conclusions: what has been done and what should be done next

Classical conditioning clearly contributes to the modulation of pain sensitivity. This modulation takes the form of both conditioned hyperalgesic responses and conditioned analgesic responses to initially neutral environmental stimuli. Importantly, the direction in which conditioned responses seem to modulate pain appears to depend on the type of CS and the belongingness between the CS and the US. Whereas contextual cues and audiovisual cues can serve as CSs for evoking hyperalgesic conditioned responses when they are paired with an exogenous opiate agonist such as morphine, these same cues seem to evoke the opposite conditioned response (i.e., an analgesic response) when they are paired with stressors that do not produce an internal malaise. Opposite to the analgesic conditioned response that contextual cues and audiovisual cues evoke after being paired with exogenous and endogenous opiates, olfactory and gustatory CSs paired with stressors (including internal malaise) seem to produce hyperalgesia.

It is by now widely accepted that changes in unconditioned stress-induced analgesia are due at least in part to the release of endogenous opiates, gamma-aminobutyric acid (GABA), and endocanabinoids (for a review, see Ford & Finn, 2008). However, an asymmetry is seen regarding the study of neural pathways and neurotransmitters involved conditioned stress-induced analgesia in that research here has focused largely on the role of endogenous opiates. Further research is needed to better understand the contribution of GABA and other neurochemicals in conditioned stress-induced analgesia.

Although the research regarding conditioned analgesia and hyperalgesia has produced a large number of reports concerning animal models, less frequent are reports in which human participants were used, and far scarcer yet are the reports that used clinical populations in which adequate controls were used to assess the role of associative factors. While many clinical and preclinical studies have detected tolerance to exogenous opiates relative to controls or baselines (e.g., Angst, Koppert, Pahl, Clark, & Schmelz, 2003; Chia, Liu, Wang, Kuo, & Ho, 1999; Chu, Clark, & Angst, 2006; Compton, 1994; Compton, Charuvastra, Kintaudi, & Ling, 2000; Doverty et al., 2001; Guignard et al., 2000; Hood, Curry, & Eisenach, 2003; Koppert et al., 2003), none of these studies looked for contextual control of hyperalgesia or tolerance to morphine-induced analgesia. Moreover, clinical and preclinical studies need to incorporate experimental variables and associative factors that resemble ecologically valid settings. Preclinical and clinical research must be conducted to assess the ecological validity of the findings from the associative literature conducted in animal models.

Applications of some of the effects discussed in this review include manipulations to minimize tolerance during long-term treatment with analgesics and behavioral manipulations that could augment pharmacological treatment of acute pain and pain syndromes. One concern in conducting translational research is that the effect sizes from experiments that used animal models might not transfer to preclinical and clinical studies. Toward addressing this issue, experiments using animal models should focus more on preparations that might increase the magnitude of the conditioned response. Specifically, basic research needs to identify procedures that are able to increase the effect of

conditioned stress-induced analgesia. For example, *superconditioning* (i.e., augmented responding observed after reinforced training of the target CS in compound with a inhibitory CS; Rescorla, 1971), which has been used to increase low effect size of conditioned responses of the immune system (e.g., Vogel, Castro, Solar, & Soto, 2007), might be employed. Similarly, basic research focusing on the reduction of tolerance to morphine-induced analgesia might also provide useful insights concerning procedures that could help in the alleviation of pain while using an opiate medication. For example, procedures that produce deeper extinction (e.g., Urcelay, Lipatova, & Miller, 2009; Urcelay, Wheeler, & Miller, 2009) prevent the recovery of an extinguished response (e.g., Denniston, Chang, & Miller, 2003; Miguez, Witnauer, Laborda, & Miller, in press) or prevent the development of tolerance (e.g., Siegel, 1977) need to be assessed through basic research on tolerance to morphine analgesia before investigators conduct research on preclinical and clinical subjects.

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