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Research Article

Effects of Acute and Sustained Pain Manipulations on Performance in a Visual-Signal Detection Task of Attention in Rats

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ABSTRACT Patients with pain often display cognitive impairment including deficits in attention. The visual-signal detection task (VSDT) is a behavioral procedure for assessment of attention in rodents. Male Sprague Dawley rats were trained in a VSDT and tested with three different noxious stimuli: (i) intraperitoneal injection of lactic acid; (ii) intraplantar injection of formalin; and (iii) intraplantar injection of complete Freund's adjuvant (CFA). The muscarinic acetylcholine receptor antagonist, scopolamine was also tested as a positive control. Scopolamine (0.01–1.0 mg/kg) dose dependently reduced accuracy and increased response latencies during completed trials with higher scopolamine doses increasing omissions. Lactic acid (0.56–5.6% ip) also increased response latencies and omissions, although it failed to alter measures of response accuracy. Formalin produced a transient decrease in accuracy while also increasing both response latency and omissions. CFA failed to alter VSDT performance. Although VSDT effects were transient for formalin and absent for CFA, both treatments produced mechanical allodynia and paw edema for up to 7 days. These results support the potential for noxious stimuli to produce a pain-related disruption of attention in rats. However, relatively strong noxious stimulation appears necessary to disrupt performance in this version of the VSDT. Drug Dev Res 76 : 194–203, 2015.

Key words: attention; pain; lactic acid

INTRODUCTION

The principal measures of pain in humans consist of verbal reports structured by instruments such as visual analog scales of pain severity [Melzack and Katz, 2006]. However, noxious stimuli that elicit verbal reports of pain in humans also produce changes in nonverbal behavior in both humans and animals, and these nonverbal pain-related behaviors serve both as clinically relevant endpoints in pain assessment and as dependent measures in preclinical pain research [Negus et al., 2006; Mogil, 2009; Whiteside et al., 2013]. One category of pain-related changes in behavior is impairment of cognitive func-

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tion. Cognition embraces a range of processes that include attention, perception, working memory, long-term memory, executive function, language, and social cognition [Keeler and Robbins, 2011], and pain has the potential to commandeer finite cognitive resources and reduce their availability for processing other stimuli. For example, chronic pain reduces measures of attention in humans [Eccleston, 1994; Crombez et al., 1997; Lorenz et al., 1997; Eccleston and Crombez, 1999; Grace et al., 1999] and rodents [Boyette-Davis et al., 2008; Pais-Vieira et al., 2009].

The visual-signal detection task (VSDT) is a procedure used to assess attention in rats [Parasuraman, 1984], and versions of the VSDT have been used to study effects of various manipulations on attention-related behavior [Bushnell et al., 1997; Rezvani and Levin, 2004; Hillhouse and Prus, 2013]. The goal of this study was to assess changes in VSDT performance of rats produced by three different pain stimuli: (i) intraperitoneal injection of dilute lactic acid; (ii) bilateral intraplantar injection of formalin; and (iii) bilateral intraplantar injection of complete Freund's adjuvant (CFA).

Intraperitoneal injection of dilute acid is an acute noxious stimulus that produces transient (~1 h) stimulation of a stretching response as well as transient depression of positively reinforced operant responding in an assay of intracranial self-stimulation (ICSS) [Pereira Do Carmo et al., 2009]. Intraplantar formalin also stimulates robust expression of acute pain behaviors (i.e., paw flinching and licking) for approximately 1 h after administration, and these initial effects are followed by a more sustained ($\geq$2 weeks) period of paw inflammation, necrosis, and neuropathy accompanied by hypersensitive withdrawal reflexes to thermal and mechanical stimuli and depression of ICSS [Vierck et al., 2008; Grace et al., 2014; Leitl et al., 2014]. Intraplantar CFA elicits fewer acute pain behaviors immediately after its injection, but like formalin, it produces paw inflammation and sustained thermal/mechanical hypersensitivity, and it also produces significant but more transient (~1 day) depression of wheel running and ICSS in rats [Vierck et al., 2008; Grace et al., 2014]. Thus, the noxious stimuli evaluated here differed in the intensity of acute pain behaviors (acid = formalin > CFA) and the duration of more sustained signs of pain such as mechanical hypersensitivity (formalin = CFA > acid). As a positive control, effects of these noxious stimuli were compared with effects produced by the muscarinic acetylcholine receptor antagonist, scopolamine, which impairs attention in humans [Lenz et al., 2012] and VSDT performance in rats [Bushnell et al., 1997; Rezvani et al., 2009].

MATERIALS AND METHODS

Subjects

Seventeen adult, male Sprague-Dawley rats (Harlan, Fredrick, MD, USA) were individually housed and maintained on a 12-h light/dark cycle with lights on from 6:00 a.m. to 6:00 p.m. All rats were given restricted access to food to maintain 85% of their ad libitum weights. Rats had free access to water in their home cages. Animal maintenance and research were in compliance with National Institutes of Health guidelines on the care and use of animal subjects in research. All animal use protocols were approved by the Virginia Commonwealth University Institutional Care and Use Committee.

Compounds

Scopolamine HCl (Sigma-Aldrich, St. Louis, MO) was dissolved in saline for intraperitoneal (i.p.) injection in a volume of 1 ml/kg, and doses are expressed as the salt. Lactic acid (Spectrum Chemical, Gardena, CA) was diluted in bacteriostatic water for i.p. injection in a volume of 1 ml/kg. Formalin (Fisher Scientific, Waltham, MA; diluted in saline to a 5% concentration) and CFA (Sigma-Aldrich) were administered in 100-μl bilateral injections into the plantar aspect of the left and right hind paws using a 27-g needle.

VSDT Apparatus

Experiments were conducted in six identical operant chambers enclosed in sound attenuating cabinets equipped with a fan for ventilation and background noise (Med-Associates Inc., St. Albans. VT). Each operant chamber was equipped with a round signal light (2.5 cm in diameter), a houselight, two retractable levers, and a food pellet dispenser. The signal light was positioned in the center of the front panel between the response levers and above the food receptacle. Signal light intensity was adjusted using a fader control that allowed for four different illumination levels (i.e., background illumination and three signal intensities; ENV-226A, Med-Associates Inc.). Both background and signal illuminations were calibrated using a light meter (LX1330B, HisGadget, Union City, CA). Data were collected using Med PC version 4.1 (Med-Associates Inc.).

Training

After initial lever-press training, rats were trained according to procedures adapted from previously published studies [Bushnell, 1999; Rezvani and Levin, 2004; Rezvani et al., 2009; Hillhouse and

Prus, 2013]. Under the terminal schedule, daily sessions consisted of 180 trials divided into a randomized sequence of 90 "blank" trials and 90 "signal" trials. During blank trials, food was delivered only after responding on one lever (the "blank" lever), whereas during signal trials, food was delivered only after responding on the other lever (the "signal" lever). The assignment of left and right levers as the blank and signal levers was counterbalanced across rats. At the beginning of each trial, the levers were in the retracted position, the house light was on, and the signal light was illuminated at the low background intensity (0.6 lux). Each trial lasted 4.5–18.5 s and began with a prestimulus delay of 3, 6, or 12 s (30 blank trials and 30 signal trials with each delay, presented in randomized sequence). Subsequently, the "blank" or "signal" stimulus was delivered for 500 ms. During blank trials, there was no change in intensity of the signal light. During signal trials, the signal light intensity increased by 1.8 lux above background illumination. This stimulus was followed by a 1 s poststimulus delay, extension of the levers, and initiation of a response period. The trial ended and levers were retracted after a lever response was emitted or after 5 s had elapsed, whichever occurred first. If a correct response occurred during the response period (i.e., response on the blank lever during a blank trial or on the signal lever during a signal trial), then lever retraction was accompanied by delivery of a food pellet. Conversely, if an incorrect response occurred, then lever retraction was accompanied by initiation of a 2 s time out, during which both the house light and signal light were turned off. Outcomes of each trial were designated as follows: a correct response was designated as a "hit" during a signal trial and a "correct rejection" during a blank trial; an incorrect response was designated as a "miss" on a signal trial and a "false alarm" on a blank trial; and failure to emit a response within 5 s was considered an "omission." Training was considered complete when a rat responded correctly for at least 70% of both blank and signal trials for 3 consecutive days.

Testing

Once training was complete, test sessions were initiated. These were identical to the training sessions, with the exception that signal intensity during signal trials increased by one of three different values (0.6, 1.2, or 1.8 lux) rather than only the highest value of 1.8 lux. Thus, test sessions consisted of 90 blank trials and 30 trials for each of the three signal intensities (equaling 90 total signal trials). Test sessions were used to evaluate effects of four different experimental manipulations. Scopolamine (0.01–1.0 mg/kg i.p.) was tested as a positive control to confirm sensitivity of the procedure to effects of a muscarinic acetylcholine receptor antagonist as reported in previous studies [Bushnell et al., 1997]. Subsequently, three different noxious stimuli were tested: i.p. injection of dilute lactic acid (0.56–5.6% in distilled water and delivered in a volume of 1.0 ml/kg), bilateral intraplantar injection of formalin (5% in saline; 100 μl to each hind paw), or CFA (100 μl to each hind paw). Scopolamine (20 min pretreatment) was tested in a group of six experimentally naïve rats, and lactic acid (0 min pretreatment) was tested in a group of seven rats (six experimentally naïve, one from scopolamine group). Test sessions for scopolamine occurred twice a week (typically Tuesdays and Fridays) with at least 2 days separating each test, whereas tests with lactic acid occurred only once a week to minimize the potential for tissue damage associated with closely spaced injections. A training session was always conducted on the day immediately preceding a test session, and the sequences of scopolamine and lactic acid doses were randomized across rats in a Latin square design. Formalin was tested in a group of five rats (one experimentally naïve and four from scopolamine group). Data for the naïve rat fell within the range of results obtained for the other animals on most endpoints, including endpoints that revealed significant effects, so text below reports combined results for all five rats. CFA was tested in a group of nine rats (four experimentally naïve and five from i.p. acid group). The results of statistical analyses were identical whether data from these two groups were analyzed separately or together, so the text below reports combined results for all nine rats. In each group, rats were first treated with bilateral intraplantar saline and tested 15 min later to determine vehicle effects. At least two days later, rats were treated with bilateral formalin or CFA, and testing was conducted 15 min, 3 days and 7 days after treatment. The doses and pretreatment times for scopolamine were based on previous studies of scopolamine effects on performance of attention tasks in rats [Milar, 1981; Bushnell et al., 1997; Rezvani et al., 2009]. The doses and pretreatment times for lactic acid, formalin, and CFA were based on previous studies on pain-stimulated and pain-depressed behavior [Pereira Do Carmo et al., 2009; Leitl et al., 2014].

Paw Swelling and Mechanical Allodynia

Paw width and paw withdrawal threshold from von Frey filaments were measured before and 7

days after formalin or CFA treatment to provide independent measures of inflammation-associated swelling and mechanical allodynia after these treatments. For paw width, dorsal-ventral thickness of the left hind paw was measured to the nearest 0.01 mm with electronic digital calipers (Traceable Calipers, Friendswood, TX). The von Frey filament test was used to measure sensitivity to a punctate pressure stimulus. Rats were placed on an elevated mesh galvanized steel platform in individual chambers with a hinged lid and allowed to acclimate for at least 20 min. Subsequently, von Frey filaments (0.4–15 g in approximate 0.25 log increments; North Coast Medical, Morgan Hill, CA) were applied to the plantar aspect of the left hind paw using the "up-down" method to determine log median withdrawal threshold [Chaplan et al., 1994]. Paw thickness and mechanical sensitivity were assessed for each rat on day 0 (before intraplantar formalin or CFA injection) and day 7 (after the last test in the VSDT). Data for paw width and mechanical allodynia before and after formalin or CFA were compared by paired *t*-test, and the criterion for significance was $P < 0.05$.

Statistical Analysis

The following dependent variables were used: (i) percent hits for each signal intensity and for all signal trials combined; (ii) percent correct rejections for blank trials; (iii) response latency for signal and blank trials; and (iv) response omissions for signal and blank trials. Percent hits for each signal intensity, and for all signal intensities combined, was calculated as (number of correct responses on signal trials ÷ number of signal trials completed) *100. Percent correct rejections was calculated as (number of correct responses on blank trials ÷ number of blank trials completed) *100. Response latency for completed trials was defined as the average time elapsed between lever extension and occurrence of a response during completed trials (determined separately for signal and blank trials). Omissions were defined as total number of trials during which no response occurred (determined separately for signal and blank trials). All data were reported as means ± the standard error of the mean (SEM). Data were analyzed by one- or two-factor repeated-measures analysis of variance (ANOVA), and a significant ANOVA was followed by a Dunnett's or Newman–Keuls post hoc test depending on the desired comparison. The criterion for significance was $P < 0.05$. All statistical analyses were conducted using GraphPad Prism 6.0 for Windows (La Jolla, CA).

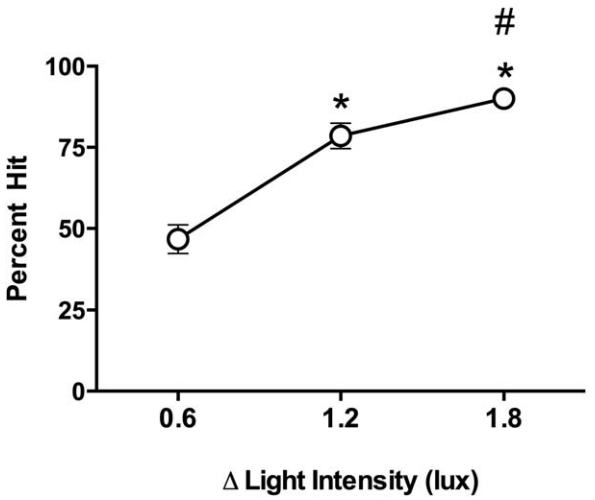

Fig. 1. The effects of vehicle treatment on response accuracy during signal trials. Abscissa: Change in signal light intensity in lux. Ordinate: response accuracy quantified as percent hit. Statistically significant effects of light intensity are noted. *$P < 0.05$ versus 0.6 (lux); #$P < 0.05$ versus 1.2 (lux) as determined by one-way ANOVA followed by Newman–Keuls post hoc test. All data show mean ± SEM for 17 rats. Data are collapsed across all types of vehicle treatment used in this study: i.p. saline for scopolamine ($N = 6$), i.p. water for lactic acid ($N = 6$), bilateral intraplantar saline for both formalin and CFA ($N = 5$). In cases where a rat was used to test two manipulations (e.g., scopolamine and formalin), then only the first vehicle test was included in this analysis. Vehicle control data for each group are shown in Figure 2.

RESULTS

Baseline Performance in the VSDT

To provide an overview of baseline performance in the VSDT, Figure 1 shows performance during signal trials after vehicle treatment for all 17 rats in the study. There was a significant main effect of signal intensity [$F(2,32) = 70.75$, $P < 0.0001$]. Newman–Keuls post hoc testing indicated that accuracy of performance, quantified as percent hits, was intensity-dependent such that accuracy increased with each increase in signal intensity. When collapsed across all signal intensities, mean ± SEM percent hit during signal trials was 72.04 ± 11.51, and the mean ± SEM percent correct rejections during blank trials was 88.68 ± 5.71. Average response latencies during signal and blank trials were 0.38 ± 0.13 s and 0.42 ± 0.13 s, respectively, and the average numbers of response omissions was 0.11 ± 0.33 for both signal and blank trials.

Effects of Scopolamine, Lactic Acid, Formalin, and CFA on Response Accuracy

Figure 2 shows effects of scopolamine (0.01–1.0 mg/kg) on accuracy of performance at each signal

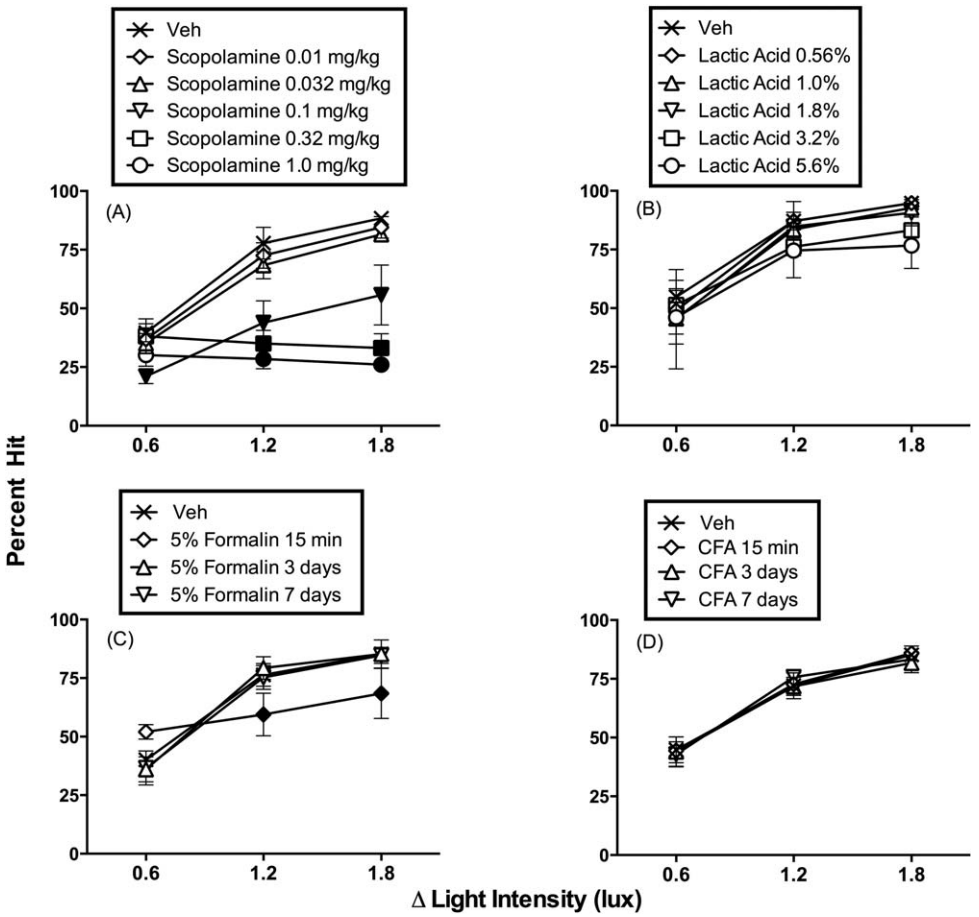

Fig. 2. The effects of (**A**) scopolamine, (**B**) lactic acid, (**C**) formalin, and (**D**) CFA on response accuracy during signal trials. Abscissae: Change in signal light intensity in lux. Ordinates: response accuracy quantified as percent hits. Filled points show doses at which percent hits were statistically different from vehicle as determined by two-way ANOVA followed by Dunnett's post hoc test, $P < 0.05$. All data show mean ± SEM for five–nine rats.

intensity during signal trials. Two-way ANOVA indicated main effects of dose [$F(5, 25) = 13{,}98$; $P < 0.0001$] and signal intensity [$F(2, 10) = 40.58$; $P < 0.0001$], and a significant interaction [$F(10, 50) = 11.58$; $P < 0.0001$]. Scopolamine dose-dependently reduced response accuracy during signal trials (i.e., percent hit), and this effect was strongest for higher response accuracies maintained by higher signal intensities.

Figure 2 also shows effects of all three noxious stimuli on accuracy of performance at each signal intensity. Two-way ANOVAs indicated main effects of signal intensity ($P < 0.0001$ for all groups), but there was not a main effect for acid concentration [$F(5, 30) = 1.344$; $P = 0.2729$], time after formalin [$F(3, 12) = 0.6816$; $P = 0.5801$], or time after CFA [$F(3, 24) = 0.1043$; $P = 0.9568$]. The interaction was also not significant between signal intensity and either acid concentration [$F(5, 30) = 1.344$; $P = 0.2729$] or time after CFA [$F(6, 48) = 0.452$; $P = 0.8586$]. There was a significant interaction between signal intensity and time after formalin [$F(6, 24) = 3.780$; $P = 0.0086$], and Dunnett's post hoc test indicated a significant decrease in response accuracy at the highest two signal intensities 15 min after formalin treatment.

Figure 3 shows effects of scopolamine and noxious stimuli on response accuracy for all signal trials combined and for blank trials, and one-way ANOVA results for each trial type are shown in Table 1. Scopolamine reduced response accuracy during both signal trials and blank trials. Conversely, neither lactic acid nor CFA altered accuracy during either signal trials or blank trials. Formalin also failed to alter response accuracy during signal trials when data were collapsed across all signal intensities; however, formalin did reduce accuracy during blank trials, and Dunnett's post hoc test indicated a significant decrease in accuracy after 15 min.

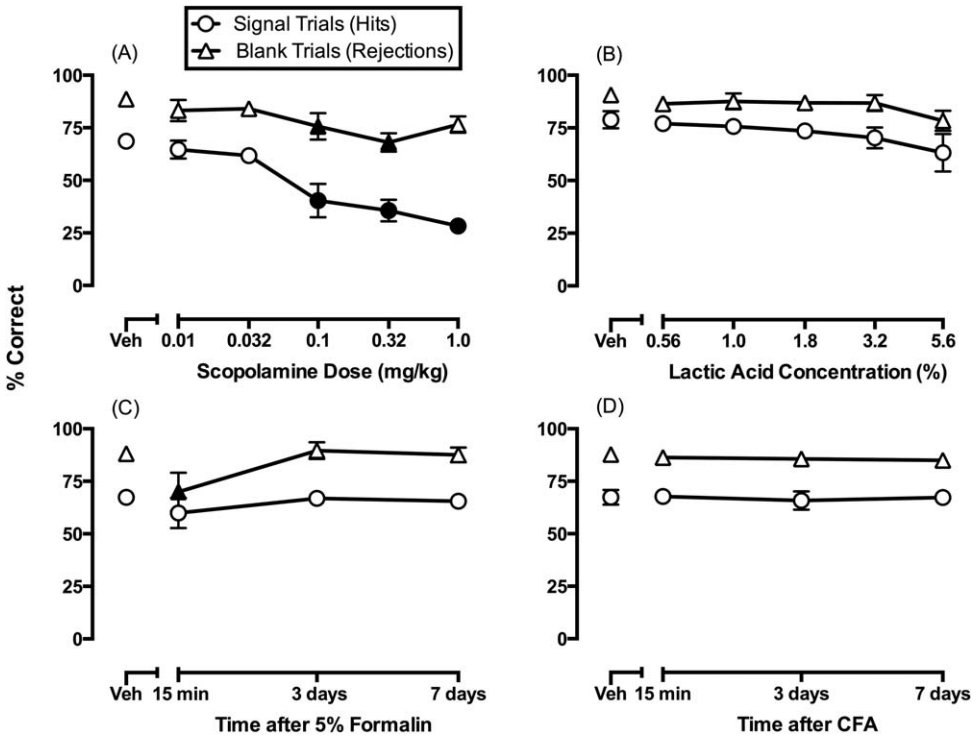

Fig. 3. The effects of (**A**) scopolamine, (**B**) lactic acid, (**C**) formalin, and (**D**) CFA on response accuracy for signal and blank trials. Abscissae: dose, concentration or pretreatment time of the compounds. Ordinates: response accuracy quantified as % correct across all signal trials or all blank trials. Filled points show doses, concentrations or times at which % correct were statistically different from vehicle as determined by one-way ANOVA followed by the Dunnett's post hoc test, $P < 0.05$. All data show mean ± SEM for five–nine rats.

TABLE 1. One-way ANOVA Results for Data Shown in Figures 3 and 4

	Scopolamine	Lactic acid	Formalin	CFA
% Correct				
Signal	$F(5, 25) = 13.85$ $P < 0.0001$	$F(5, 30) = 1.795$ $P = 0.1440$	$F(3, 12) = 0.6961$ $P = 0.5721$	$F(3, 24) = 0.1127$ $P = 0.9518$
Blank	$F(5, 25) = 5.027$ $P = 0.0025$	$F(5, 30) = 2.129$ $P = 0.0892$	$F(3, 12) = 5.110$ $P = 0.0166$	$F(3, 24) = 0.5480$ $P = 0.6543$
Latency				
Signal	$F(5, 25) = 12.63$ $P < 0.0001$	$F(5, 30) = 5.658$ $P = 0.0009$	$F(3, 12) = 2.285$ $P = 0.1310$	$F(3, 24) = 2.121$ $P = 0.1241$
Blank	$F(5, 25) = 12.53$ $P < 0.0001$	$F(5, 30) = 5.671$ $P = 0.0009$	$F(3, 12) = 8.995$ $P = 0.0021$	$F(3, 24) = 2.015$ $P = 0.1387$
Omissions				
Signal	$F(5, 25) = 11.28$ $P < 0.0001$	$F(5, 30) = 28.94$ $P < 0.0001$	$F(3, 12) = 2.686$ $P = 0.0936$	$F(3, 24) = 0.5348$ $P = 0.6629$
Blank	$F(5, 25) = 10.20$ $P < 0.0001$	$F(5, 30) = 48.28$ $P < 0.0001$	$F(3, 12) = 4.469$ $P = 0.0251$	$F(3, 24) = 1.706$ $P = 0.1925$

Effects of Scopolamine and Noxious Stimuli on Response Latencies and Omissions

Figure 4 shows effects of scopolamine and noxious stimuli on measures of response latency and omissions, and one-way ANOVA results for each trial type are shown in Table 1. Both scopolamine and lactic acid dose-dependently increased response latencies and omissions during both signal and blank trials. Formalin also increased mean response latencies and omissions after 15 min, but this effect was significant only during blank trials, and formalin had no effect after 3 or 7 days. CFA had no effect at any time on either response latencies or omissions during either signal or blank trials.

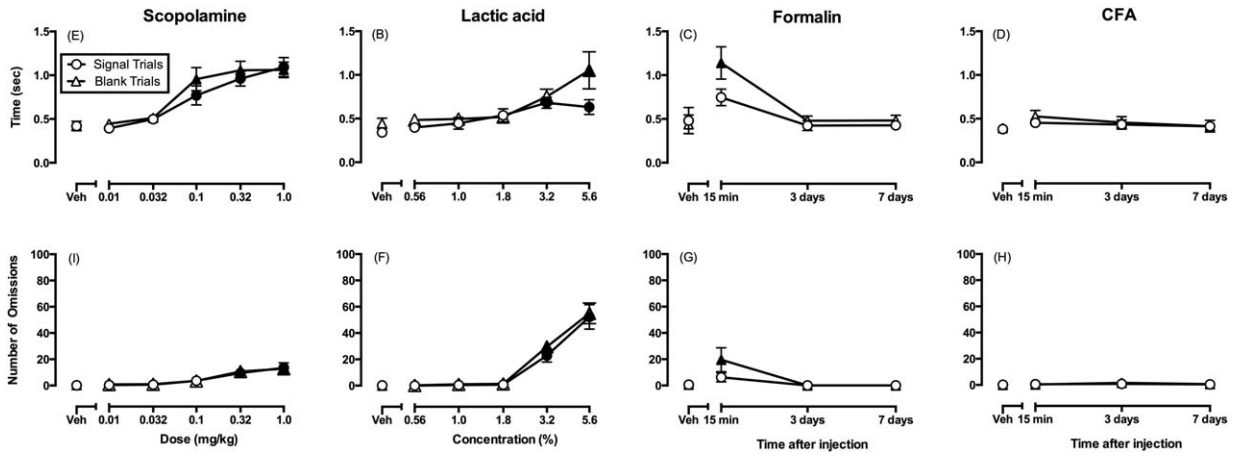

Fig. 4. The effects of (**A**, **E**) scopolamine, (**B**, **F**) lactic acid, (**C**, **G**) formalin, and (**D**, **H**) CFA on response latencies (upper panels) and omissions (lower panels). Abscissae: dose, concentration or pretreatment time of the compounds. Ordinates: response latency (s, panels A–D) or number of omissions (panels E–H). Filled points show doses, concentrations or times at which response latency or number of omissions were statistically different from vehicle as determined by one-way ANOVA followed by the Dunnett's post hoc test, $P < 0.05$. All data show mean ± SEM for five–nine rats.

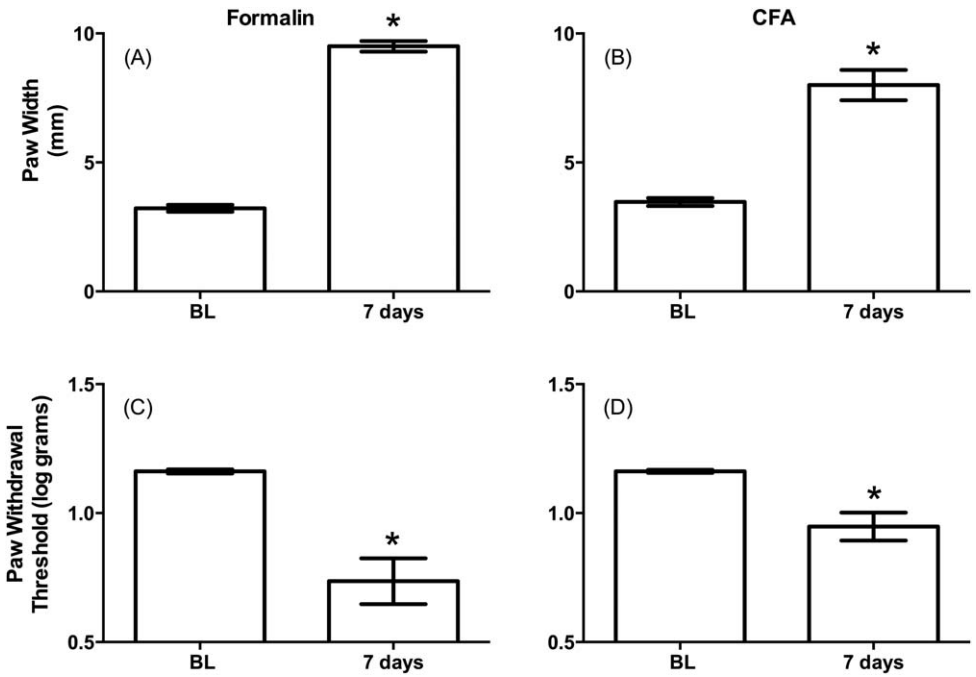

Fig. 5. The effects of (**A**, **C**) formalin and (**B**, **D**) CFA on paw swelling and mechanical sensitivity. Abscissae: time before (baseline; BL) or seven days after formalin or CFA treatment. Ordinates: paw width in mm (**A**, **B**) or paw withdrawal threshold in log grams (**C**, **D**). Asterisks indicate that both formalin and CFA produced paw swelling [$t(4) = 45.09$, $P < 0.0001$ and $t(8) = 8.632$, $P < 0.0001$, respectively] and mechanical allodynia [$t(4) = 4.785$ $P = 0.0087$ and $t(8) = 3.933$, P 0.0043, respectively] as assessed seven days after formalin or CFA treatment. All data show mean ± SEM for five–nine rats.

Paw Swelling and Mechanical Allodynia After Formalin and CFA

Figure 5 shows that both CFA and formalin treatments produced significant paw swelling and mechanical allodynia 7 days after treatment.

DISCUSSION

Effects of Signal Intensity and Scopolamine Treatment

The results agree with previous reports that response accuracy in VSDT procedures is dependent

on signal intensity and impaired by scopolamine pretreatment [Bushnell et al., 1997; Rezvani et al., 2009]. For example, in this study, scopolamine displayed similar potencies to reduce accuracy and increase response latency during both signal and blank trials, and it had threefold weaker potency to increase response omissions. An identical profile of scopolamine effects was reported by Bushnell et al. [1997] in a VSDT procedure using slightly different parameters for background and signal light intensities. Scopolamine also impaired accuracy of performance in other assays of attention in rodents, including a five-choice serial reaction time task [Mishima et al., 2002], and it has also been found to impair measures of attention in human tests [Ellis et al., 2006]. These findings confirm the sensitivity of VSDT performance in this study to an established positive control, and these scopolamine effects also provide a context for evaluating effects of noxious stimuli.

Effects of Noxious Stimuli

Two of the three noxious stimuli tested in this study also altered VSDT performance. Each noxious stimulus will be discussed in turn. First, i.p. lactic acid administration increased both response latencies and omissions in this study, but unlike scopolamine, i.p. acid failed to significantly alter response accuracy during either signal or blank trials. Similar concentrations of i.p. acid in rats have also been reported to depress operant responding for electrical brain stimulation in an ICSS procedure and to stimulate a stretching response [Pereira Do Carmo et al., 2009]. Moreover, both acid-induced depression of ICSS and stimulation of stretching appear to be related to pain, because both effects are blocked by clinically effective analgesics including the mu opioid agonist morphine and the nonsteroidal anti-inflammatory drug ketoprofen [Pereira Do Carmo et al., 2009; Negus, 2013; Rosenberg et al., 2013]. Overall, these results suggest that pain-like effects produced by i.p. acid administration in rats are sufficient to produce a nonselective decrease in operant behavior but not to produce a disruption in response-accuracy measures of attention in the VSDT procedure.

Of the three noxious stimuli tested here, intraplantar formalin produced a transient disruption of VSDT performance that most closely resembled the effects of scopolamine. Thus, when tested 15 min after administration, intraplantar formalin produced a small but significant decrease in response accuracy during both signal and blank trials as well as a significant increase in response latency during blank trials. However, four caveats warrant mention. First, the effects of formalin on response accuracy were relatively small insofar as their magnitude was less than or equal to the magnitude of effects produced by the intermediate dose of 0.1 mg/kg scopolamine. In particular, during signal trials, formalin-induced disruption was significant only when evaluated at the highest two signal intensities (Fig. 2), and this effect did not achieve statistical significance when collapsed across all signal intensities (Fig. 3). Second, in contrast to the effects of the intermediate scopolamine dose, the formalin-induced decrease in accuracy was accompanied by a significant increase in omissions during blank trials. Third, the formalin effects were transient, and were not evident 3 or 7 days after formalin administration. This corresponds to the period of the "first and second phases" of the formalin response (1–2 h after formalin administration) during which rats display vigorous paw flinching and licking responses [Tjølsen et al., 1992; Fu et al., 2001; Abbott et al., 2002]. However, disruptions in VSDT performance were not evident at later times when paw edema, mechanical allodynia, and depression of ICSS are present [this study; Fu et al., 2001; Grace et al., 2014]. Finally, the present results agree with a previous report that intraplantar formalin disrupted performance in a five-choice serial reaction time task in rats when testing occurred immediately after formalin injection [Boyette-Davis et al., 2008]. However, in that study, formalin increased omissions but did not affect either response accuracy or response latency. Taken together, these results suggest that intraplantar formalin is sufficient to produce a transient and scopolamine-like disruption in performance, but the more sustained manifestations of pain-like behavior produced by formalin do not produce sustained disruption of any measure of VSDT performance.

Lastly, intraplantar CFA failed to alter any measure of VSDT performance. Again, this lack of effect cannot be attributed to inadequate CFA dosing, because this CFA treatment did produce sustained paw edema and mechanical allodynia, and similar CFA treatments have also been shown to produce transient decreases in ICSS and more sustained decreases in wheel running in rats [this study; Grace et al., 2014; Leitl et al., 2014]. These results with intraplantar CFA differ from those in a previous study that found both decreased accuracy and increased omissions for 10 days after intra-articular administration of CFA in rats responding under a five-choice serial reaction time task [Pais-Vieira et al., 2009]. This difference may reflect greater sensitivity of the five-choice serial reaction time task than the

VSDT to sustained pain, greater intensity of pain after intra-articular than intraplantar CFA, or other procedural differences (e.g., strain of rat studied: Sprague-Dawley vs. Lister hooded). However, CFA effects in that study were not blocked by the clinically effective nonsteroidal anti-inflammatory drug carprofen that did block mechanical allodynia, suggesting that effects of CFA on performance may not have been related to pain. Results of this study do not provide evidence for a CFA-induced disruption of attention.

CONCLUSIONS

In this study, both i.p. lactic acid and bilateral intraplantar formalin functioned as noxious stimuli that acutely disrupted performance in a VSDT that has been used to assess modulators of attention in rats. These results may be related to clinical observations of pain-related disruption of attention in humans; however, the profiles of effects produced by i.p. acid and intraplantar formalin were transient and occurred during the time of maximal nociceptor activation and maximal stimulation of pain-related behaviors (i.e., the stretching response after i.p. acid or paw flinching/licking responses after i.pl. formalin). Notably, disruptions in VSDT performance were not evident at later times after formalin treatment, or at any time after i.pl. CFA treatment, despite the presence of both paw edema and mechanical hypersensitivity. As such, these results suggest that relatively strong activation of nociceptive pathways is required to disrupt performance in this version of the VSDT.

CONFLICTS OF INTEREST

None declared

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