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Lipopolysaccharide and interleukin-1β decrease sucrose intake but do not affect expression of place preference in rats

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Abstract

Immune system activation has been shown to induce decreased interest in pleasurable stimuli. Studies of this phenomenon have assessed the effect of cytokines or lipopolysaccharide (LPS) on behavior maintained by primary reinforcers, stimuli, such as palatable solutions, that effectively reinforce behavior without prior training. The studies reported in this paper replicated findings of immune system activation decreasing intake of a palatable solution and assessed the effects of immune activation on behavior maintained by a conditioned reinforcer, a stimulus paired with a the palatable solution. Using a conditioned place preference procedure, the effects of LPS and interleukin-1β (IL-1β) on sucrose intake (primary reinforcer) and preference for a sucrose-paired environment (conditioned reinforcer) were tested. LPS and IL-1β decreased sucrose intake but had no effect on the expression of a sucrose-induced place preference, indicating a differential effect of immune system activation on appetitive behaviors maintained by primary and conditioned reinforcers. Finally, it was shown that a sucrose-induced place preference is sensitive to the motivational state of the subjects at the time of testing; a sucrose-induced place preference was demonstrated if rats were tested when water deprived but not if tested after free access to water.

Keywords: Anhedonia; Appetitive behavior; Conditioning; Immune activation; Motivation; Place preference; Reward; Sickness

1. Introduction

Immune system activity can cause profound changes in behavior. For example, administration of lipopolysaccharide (LPS), a component of the cell wall of gram negative bacteria, decreases social exploration, locomotor activity, food intake, and food-motivated behavior and increases sleep in rodents (for reviews, see Dantzer et al., 1999; Larson and Dunn, 2001). This profile of behavior change is referred to as "sickness behavior." Investigations have implicated cytokines as mediating communication between the immune system and the central nervous system (CNS) and as mediators of these behavioral effects. In fact, administration of cytokines, most notably interleukin-1β (IL-1β), results in a behavioral profile very similar to that seen when animals are given a bacterial or viral treatment (for review, see Larson and Dunn, 2001).

One aspect of sickness behavior is anhedonia, or loss of interest in pleasurable activities (Yirmiya, 1997). Assessments of the anhedonic effect of infection and inflammation in animal models have shown that LPS decreases saccharin consumption and preference (Yirmiya, 1996). Additionally, certain cytokines decrease self-administration of electrical brain stimulation (EBS) in rats (Anisman et al., 1996). Both of these paradigms (food intake and EBS) provide evidence that immune activation can disrupt behavior maintained by pleasurable stimuli, though most assessments of the anhedonic effect of immune activation have evaluated ingestive behaviors. Because immune activation also produces an anorectic effect (e.g., McCarthy et al., 1985), it is difficult to distinguish between the anhedonic effect of immune activation and the anorexia it induces (Anisman and Merali, 1999). Regardless, evaluations have determined that immune stimuli can disrupt appetitive behaviors involved in feeding (Cross-Mellor et al., 2000, 2003) and decrease behaviors maintained by pleasurable stimuli (Yirmiya, 1996) suggesting that an anhedonic effect may be induced by sickness and thus may be related to some sickness-induced anorexia.

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Studies that have assessed the effect of immune activation and cytokines on appetitive behaviors and behaviors maintained by appetitive stimuli have typically focused on changes in the approach or self-administration of primary reinforcers, stimuli that are biologically relevant to the organism and control behavior on their first presentation (e.g., palatable solutions). It is well known that initially neutral stimuli paired or associated with primary reinforcers develop reinforcing (Cardinal et al., 2003; Domjan, 1998; Williams and Dunn, 1991), and presumably hedonic, properties. The current series of experiments assessed the effect of immune activation on behavior maintained by conditioned reinforcing stimuli (i.e., stimuli associated with primary reinforcers) by evaluating the effects of LPS and IL-1β on the expression of a conditioned place preference.

In the place preference procedure animals are trained to associate a distinctive environment with a primary, unconditioned reinforcer. Since animals prefer an environment paired with reinforcing stimuli over a control environment, referred to as a place preference, this provides an indirect assessment of the development of conditioned reinforcement (e.g., Acquas et al., 1989). While the majority of place preference studies employ drugs as the unconditioned stimulus, past work has used palatable solutions as the primary, unconditioned stimulus (e.g., Agmo et al., 1995; Spiteri et al., 2000; Stefurak and van der Kooy, 1992) and the methods described in this paper were modeled after these published studies. Stefurak and van der Kooy (1992), for example, conditioned rats by exposing them to a distinctive environment in which they could consume saccharin for 20 min every other day. On alternating days, animals were exposed to another environment in which they could consume water. After 8 environment–saccharin pairings, a preference test was conducted in which animals were allowed to explore both environments in the absence of water or saccharin. They found preferences for the saccharin-paired environment that were dependent upon saccharin dose, demonstrating a saccharin-mediated place preference.

Previous work has shown that immune system activity has differential effects on various aspects of feeding. For example, Cross-Mellor et al. (2003) showed that LPS decreased voluntary sucrose intake in a traditional bottle intake test but did not affect the intake of sucrose when infused intraorally. Based on their findings, it appears that LPS does not diminish the appetitive responses to the taste of sucrose, a finding also recently shown by Aubert and Dantzer (2005). This is the case despite evidence that LPS does decrease sucrose intake. Based on such findings, it has been suggested that LPS does not affect the affective components of feeding but does affect the consummatory (intake) components (Cross-Mellor et al., 2000, 2003). Given these findings, it was expected that LPS and IL-1β may have different effects on the expression of a conditioned place preference and sucrose intake. Three experiments evaluated this. Experiment 1 and 2 assessed the effects of LPS and IL-1β on the expression of a sucrose-mediated conditioned place preference and on sucrose intake. In these studies, rats were water deprived at the time of conditioning and testing. A third experiment evaluated the effect of LPS on the expression of a conditioned place preference in rats that were water deprived during conditioning but not during testing to ensure that effects seen in Experiment 1 and 2 did not result from water deprivation at testing.

2. Methods

2.1. Subjects

Subjects were forty-four Wistar rats [Harlan, Indianapolis, IN] weighing 350–400 g. They were housed in pairs in plastic cages and maintained on a 12 h:12 h light:dark cycle. Experimental manipulations occurred during the light portion of the cycle. Animals were fed ad libitum and had restricted access to water as noted below. In the case of water restriction, rats had access to water for 4 h/day immediately after experimental manipulations. Animal protocols received approval from the Concordia College *Institutional Animal Care and Use Committee*.

2.2. Apparatus

A conditioned place preference apparatus was used in all studies. This apparatus consisted of three distinct environments, two conditioning chambers, 38 cm × 30 cm × 30 cm, and a middle choice chamber, 25 cm × 30 cm × 30 cm. One conditioning chamber was black with a rough, black plastic mat on the floor and the other was white with a smooth, clear plastic mat on the floor. Between the conditioning chambers was a smaller grey (choice) chamber with a smooth Plexiglas floor. These three chambers were separated by sliding doors allowing the apparatus to be converted from three separate chambers to one multi-colored chamber.

2.3. Injected solutions

Rats were injected with either physiological saline, lipopolysaccharide (Sigma Chemical Co., St. Louis, MO, serotype 0127:B8) or rat recombinant interleukin-1β (R&D Systems, Minneapolis, MN). Injections occurred 90 min before the onset of testing and were given intraperitoneally (i.p.). LPS was dissolved in saline to create a 50 μg/ml solution and injected at a dose of 50 μg/kg. IL-1β was dissolved in saline to create a 4 μg/ml solution and injected at a dose of 4 μg/kg. Since the ability to move throughout the place preference apparatus was necessary for testing a conditioned place preference, it was important to chose an LPS and IL-1β dose that did not depress all motor activity. These doses were chosen based on pilot studies demonstrating that they decreased food and sucrose intake, indicating a "sickness behavior" effect, without eliminating all motoric activity.

2.4. General procedure

The procedure used to induce a sucrose-mediated conditioned place preference was modeled off of previous assessments of food or palatable solutions being used to induce a place

preference (e.g., Agmo et al., 1995; Stefurak and van der Kooy, 1992).

Subjects were water deprived for 20 h daily and trained to consume an 18% sucrose solution. During training, rats were given the sucrose solution for 30 minutes/day. Sucrose consumption pretraining was done to ensure that once conditioning began rats would readily consume sucrose in the place preference apparatus. After 3 days of sucrose consumption training, place preference conditioning began.

Subjects were given a place preference pretest to measure the initial side preference. This test consisted of free exploration of the entire apparatus for 10 min. During this time, the number of seconds the rat remained in the black and white chambers were recorded. The rat was considered to be in a particular chamber as long as it had both front paws in that chamber. Motor activity was also measured during this test by counting the number of chamber crossings (i.e., each time the animal entered or exited either the black or white chamber was counted as one cross).

Twenty-four hours following the pretest, conditioning began. A biased place preference procedure was used based on previous assessments of food or palatable solutions being used to induce a place preference (Agmo et al., 1995; Spiteri et al., 2000). All subjects had access to an 18% sucrose solution while confined to the nonpreferred side of the apparatus (black or white) for 20 min. More animals, across all experiments, significantly preferred the black chamber during the pretest ($\chi^2=9.09$, $p<0.05$) and thus, for the majority of animals, the sucrose-paired side was the white environment. Sucrose conditioning sessions occurred eight times on alternating days. On the other 8 days, subjects were confined to the preferred side of the apparatus for 20 min with water available. This means that all animals were equally exposed to both their nonpreferred (sucrose-paired) and preferred (water-paired) side of the apparatus during conditioning. Liquid solutions were presented in graduated tubes with angled stoppers and placed in the same corner of the apparatus during each conditioning trial (Stefurak and van der Kooy, 1992).

Following the 16 conditioning days, post-conditioning place preference tests were conducted. Like the pretest, this consisted of free exploration of the entire apparatus for 10 min and the number of seconds the animal spent in the black and white chamber was recorded. In addition, motor activity was measured by counting the number of chamber crossings. Immediately after the post-test, all animals had access to the 18% sucrose solution in a transfer cage, similar to their home cage, for 10 min. Forty-eight hours after the first post-conditioning test, a second post-conditioning test was conducted. Prior to testing, rats were injected with either saline or LPS/IL-1β as described below.

2.4.1. Experiment 1: LPS/deprived

Sixteen rats were injected with either saline or 50 μg/kg of LPS before the first post-conditioning test. Injections were reversed for the second test. All animals in this study were water deprived for 20 h/day during pre- and post-testing and during place preference conditioning.

2.4.2. Experiment 2: IL-1β/deprived

Twelve rats were treated as Experiment 1 except that LPS was substituted with 4 μg/kg of IL-1β.

2.4.3. Experiment 3: LPS/nondeprived

Sixteen rats were treated as Experiment 1 except that they were only water deprived for 20 h/day during place preference conditioning. Pre- and post-testing occurred after 48 h of ad lib water.

2.5. Data analysis

Preference for the sucrose-paired side of the apparatus was determined by calculating the time spent in the sucrose-paired side/time spent in sucrose- and water-paired side. A conditioned place preference was also measured by comparing time spent in the sucrose-paired side during post-test to time spent in the sucrose-paired side during pretest. Sucrose consumption was determined by measuring the difference in bottle weights before and after the sucrose consumption period.

Each experiment employed a within subjects design so data analyses were conducted using repeated measures analysis of variance (ANOVA), pairwise comparisons using Bonferroni's correction, and paired sample *t*-tests. ANOVAs met Mauchley's test of sphericity. Since this was a within subjects design with some animals being tested with LPS prior to saline and vice versa, initial analyses included order of tests as a variable. This variable was not significant so reported analyses were done without using order as a variable.

Analyses were considered significant if $p<0.05$. When a *t*-test was used to determine significance for LPS and IL-1β effects on motor activity and sucrose consumption, a one tailed test was used due to the a priori prediction that LPS and IL-1β would decrease food intake and activity (for examples, see Larson and Dunn, 2001). In the case of significant *t*-tests or pairwise comparisons, effect sizes were calculated. A Cohen's $d>0.8$ was considered to be a large effect and Cohen's *d* of 0.6–0.8 was considered to be a moderate effect (Cohen, 1988). Finally, because preference data were proportionate, for analyses they were transformed using the arcsin transformation.

3. Results

3.1. Experiment 1: LPS/deprived

Fig. 1A indicates preference for the sucrose-paired side of the place preference apparatus. Rats increased preference for the sucrose-paired side of the apparatus after conditioning as seen by comparing pretest to post-test preference scores. A one-way repeated measures ANOVA conducted on these data (after arcsin transformation) revealed a marginally significant effect of test (Pretest, LPS, Saline), $F(2,30)=2.89$, $p=0.07$. Pairwise comparisons conducted on these data revealed a nonsignificant increase in preference for the sucrose-paired side of the apparatus during the saline post-test and a significant increase in preference for the sucrose side during the LPS test ($p<0.05$, Cohen's $d=0.39$). The preference for the sucrose-paired side

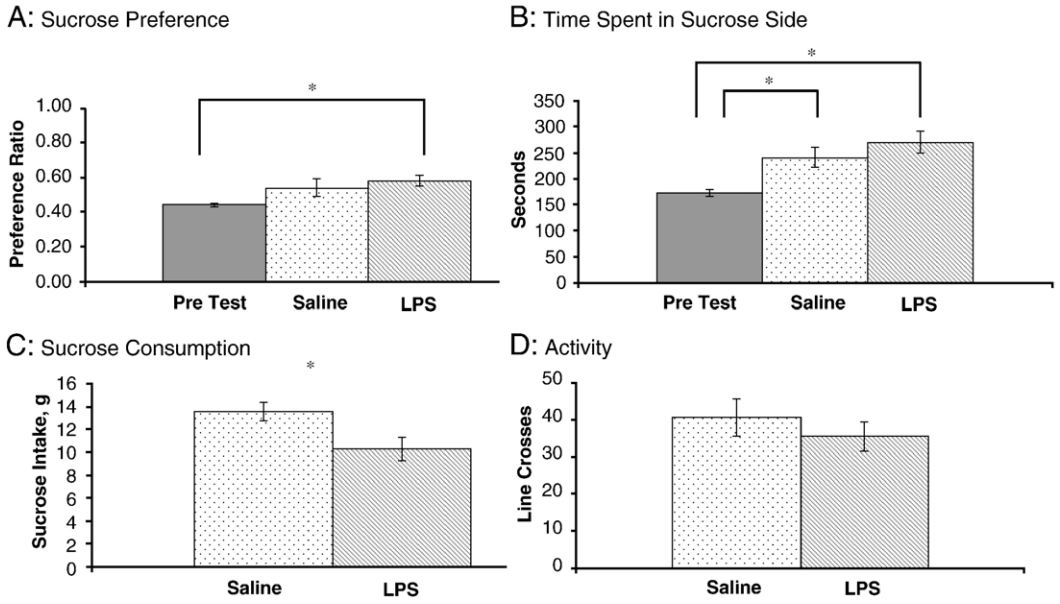

Fig. 1. This figure shows the data from Experiment 1: LPS/deprived. Panel A shows the effect of LPS on the preference for the sucrose-paired side of the place preference apparatus. Panel B shows the effect of LPS on time spent in the sucrose-paired side of the apparatus. Panel C shows the effect of LPS on sucrose intake and panel D shows the effect of LPS on motor activity. Data are presented as mean±SEM. Significant differences are indicated by asterisks.

was not disrupted by LPS, as there was no significant difference in preference for the sucrose-paired side when comparing the saline and LPS post-tests.

Fig. 1B indicates the time spent in the sucrose-paired side of the apparatus. As can be seen from this figure, rats increased time spent in the sucrose-paired side of the apparatus after conditioning. A repeated measures ANOVA conducted on these data revealed a significant effect of test, $F(2,30)=11.28$, $p<0.001$. Pairwise comparisons revealed significant increases in time spent in the sucrose-paired side of the apparatus during both the saline and LPS post-test, when compared to the pretest (Saline: $p<0.05$, Cohen's $d>0.8$; LPS: $p<0.01$, Cohen's $d>0.8$). Time spent in the sucrose-paired side was not disrupted by LPS, as there was no significant difference in time spent in the sucrose-paired side when comparing the saline and LPS post-tests.

Fig. 1C represents the amount of sucrose consumed during the saline and LPS post-test. As can be seen from this figure, LPS disrupted sucrose consumption such that animals consumed less sucrose after the LPS test than after the saline test and a *t*-test indicated this effect was significant, $t(15)=2.52$, $p<0.05$, Cohen's $d>0.8$.

Fig. 1D represents the activity level of subjects during the saline and LPS post-tests. As can be seen from this figure, LPS produced decreased activity, although a *t*-test comparing the number of chamber crossings after LPS and saline treatment failed to reach significance.

3.2. Experiment 2: IL-1β/deprived

Rats increased preference for the sucrose-paired side of the apparatus after conditioning as seen by comparing pretest to post-test preference scores (Fig. 2A). A repeated measures ANOVA conducted on these data (after arcsin transformation) revealed a significant effect of test (Pretest, IL-1β, Saline), $F(2,22)=8.51$, $p<0.01$. Pairwise comparisons revealed significant increases in preference for the sucrose-paired side of the apparatus during both the saline and LPS post-test, when compared to pretest ($p<0.05$, Cohen's $d>0.8$ for both comparisons). Preference for the sucrose-paired side was not disrupted by IL-1β and there was no significant difference in preference for the sucrose-paired side when comparing the saline and IL-1β post-tests.

Rats increased time spent in the sucrose-paired side of the apparatus after conditioning (Fig. 2B). A repeated measures ANOVA conducted on these data revealed a significant effect of test, $F(2,22)=9.59$, $p<0.001$. Pairwise comparisons revealed significant increases in time spent in the sucrose-paired side of the apparatus for the saline and IL-1β post-test, when compared to pretest ($p<0.05$, Cohen's $d>0.8$ for both comparisons). There was no significant difference in time spent in the sucrose-paired side when comparing the saline and IL-1β post-tests.

IL-1β disrupted sucrose consumption such that animals consumed less sucrose after the IL-1β test than after the saline test (Fig. 2C) and a *t*-test indicated this effect was significant, $t(11)=1.96$, $p<0.05$, Cohen's $d=0.66$.

Although IL-1β produced decreased activity in the rats, it did not eliminate all motor behavior (Fig. 2D). A *t*-test comparing the number of chamber crossings after IL-1β and saline treatment indicated significance, $t(11)=2.8$, $p<0.01$, Cohen's $d=0.78$.

3.3. Experiment 3: LPS/nondeprived

Rats increased preference for the sucrose-paired side of the apparatus after conditioning, however, this effect was minimal and rats did not demonstrate a clear preference for the sucrose-paired side of the chamber on post-testing (Fig. 3A). A

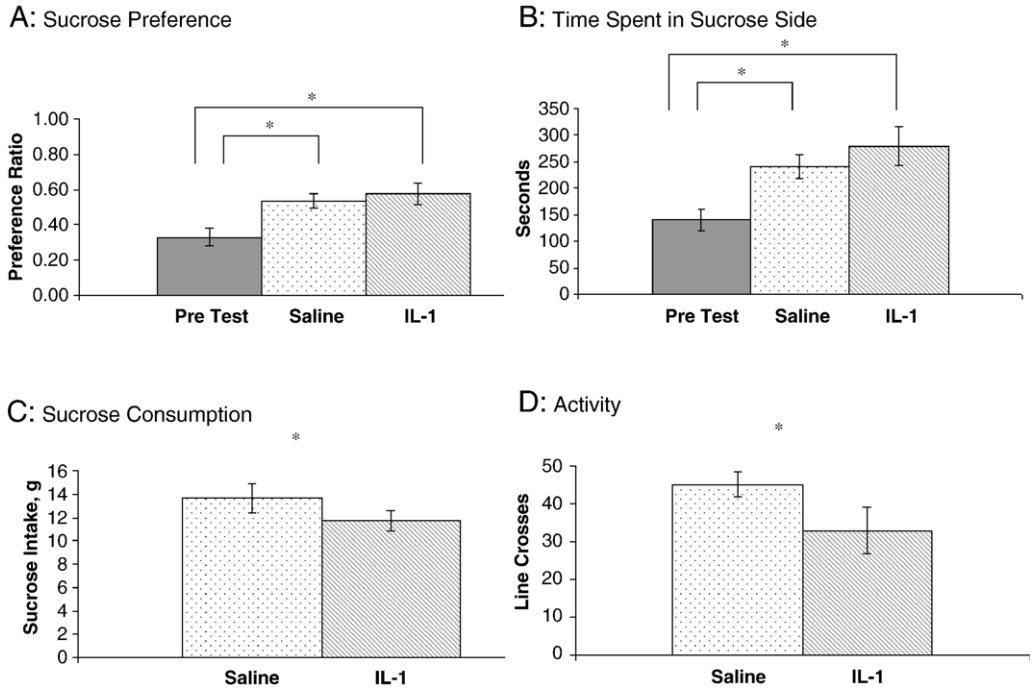

Fig. 2. This figure shows the data from Experiment 2: IL-1β/deprived. (A) Effect of IL-1β on the preference for the sucrose-paired side; (B) Effect of IL-1β on time spent in the sucrose-paired side; (C) effect of IL-1β on sucrose intake; and (D) effect of IL-1β on motor activity. Data are presented as mean±SEM. Significant differences are indicated by asterisks.

repeated measures ANOVA conducted on these data (after arcsin transformation) failed to reach significance. There was no significant difference in preference for the sucrose-paired side when comparing the saline and LPS post-tests. Rats also increased time spent in the sucrose-paired side of the apparatus after conditioning but this effect was minimal and an ANOVA conducted on these data failed to reach significance (Fig. 3B). There was no significant difference in time spent in the sucrose-paired side when comparing the saline and LPS post-tests.

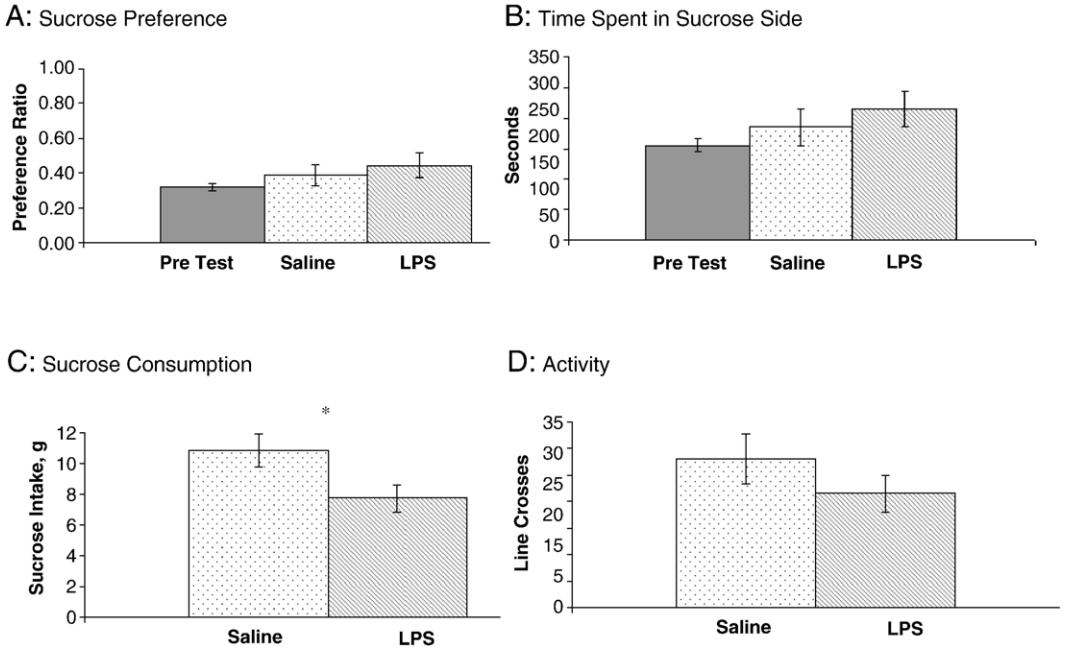

Fig. 3. This figure shows the data from Experiment 3: LPS/nondeprived. (A) Effect of LPS on the preference for the sucrose-paired side; (B) effect of LPS on time spent in the sucrose-paired side; (C) effect of LPS on sucrose intake; and (D) effect of LPS on motor activity. Data are presented as mean±SEM. Significant differences are indicated by asterisks.

LPS disrupted sucrose consumption such that animals consumed less sucrose after the LPS test than after the saline test (Fig. 3C) and a *t*-test indicated this effect was significant $t(15)=2.41$, $p<0.05$, Cohen's $d>0.8$.

Although LPS did decrease activity in the rats (Fig. 3D) a *t*-test comparing the number of chamber crossings after LPS and saline treatment failed to reach significance.

4. Discussion

These experiments demonstrated a sucrose-induced conditioned place preference in rats that were water deprived during conditioning and testing, thus confirming that a palatable solution can be used to induce a conditioned place preference (Agmo et al., 1995; Stefurak and van der Kooy, 1992). There was no difference in the expression of a place preference when animals were pretreated with either saline or LPS, or when treated with saline or IL-1β, even though LPS and IL-1β reduced consumption of the sucrose solution. Importantly, the dose of LPS used in these studies does not appear to be inherently aversive or appetitive as a separate pilot study ($n=8$, unpublished observation) showed that a one-time conditioning trial using 50 μg/kg of LPS as the unconditioned stimulus did not produce a conditioned place preference or aversion. Low doses of LPS and IL-1β were used in the current studies and it would be valuable to do a dose response assessment of the effects of LPS and IL-1β on a conditioned place preference to determine if other doses of LPS or IL-1β affect differently the expression of a place preference. Also, although exposure to each side of the place preference apparatus was controlled in these studies, all animals were conditioned with sucrose and conclusions are limited by the absence of a nonconditioned control group.

It has previously been shown that LPS *Pantoea agglomerans* can block the acquisition of a cocaine-induced place preference when subjects are pretreated with it during conditioning and prior to cocaine exposure (Suzuki et al., 1994). More recently, Nakajima et al. (2004) demonstrated that the cytokine tumor necrosis factor-α (TNF-α) blocked the acquisition of a methamphetamine-induced place preference when mice were given TNF-α before place preference conditioning. Although not tested in these current studies, LPS and cytokines may differentially affect the acquisition and expression of a place preference, an effect similar to what is seen with other CNS-active agents (e.g., Beninger and Hahn, 1983; Beninger and Herz, 1986; Sahraei et al., 2006).

In these present studies, LPS and IL-1β did not disrupt the expression of a learned response where as it has been previously demonstrated that these substances disrupt the consolidation of memory and acquisition of learned responses (e.g., Gibertini et al., 1995; Pugh et al., 2001). Thus, it appears that immune stimuli may affect the acquisition of a learned response and consolidation of memory differently than they effect the expression of learning/memory. This suggestion is supported by work demonstrating that LPS disrupted two-way avoidance learning in mice if LPS was given on day one of training but not when given on day four of training, a point at which considerable learning would have already taken place (Sparkman et al., 2005).

Since neither LPS nor IL-1β disrupted the expression of a conditioned place preference, it is speculated that immune activity may not decrease behavior maintained by conditioned hedonic stimuli, also similar to what is seen with dopamine antagonism. For example, using a runway model of food-seeking behavior, McFarland and Ettenberg (1998) found that pretreatment with haloperidol did not affect the running pattern in the presence of the food-associated stimuli, even though the doses of haloperidol are known to disrupt food reinforcement. They suggest that haloperidol and possibly other dopamine antagonists do not disrupt motivated behavior associated with conditioned stimuli but appear to disrupt the reinforcing efficacy of the primary reinforcer (McFarland and Ettenberg, 1999). Given that seeking out an environment associated with sucrose was not affected by LPS or IL-1β, yet the intake of the reinforcing sucrose solution was, it is possible that these substances may decrease the reinforcing efficacy of the primary reinforcer (i.e., the sucrose solution) without affecting motivation for the conditioned environment. This analysis must be reconciled with data demonstrating that LPS and IL-1β do have motivational effects (Aubert, 1999; Larson et al., 2002). Past research on the motivational interpretation of sickness behavior has investigated motivation for unconditioned, often hedonic, stimuli [e.g., intake of a palatable solution (Larson et al., 2002) and sexual behavior (Avitsur et al., 1997)] and future studies should evaluate more systematically how motivational effects relate to and may differ between primary and conditioned reinforcers.

An interesting observation in these studies was that if rats were not water deprived at the time of testing they failed to demonstrate a clear sucrose-induced place preference (Experiment 3) indicating that perhaps the place preference seen in Experiments 1 and 2 may be mediated by a deprivation effect. Relevant to this effect is work by Spiteri et al. (2000) who presented an elegant analysis of the different behavioral patterns in mice expressing a morphine-induced place preference and a food-induced place preference. They suggest that a food-induced place preference is more reflective of approach behaviors than affective reactions with the reverse being true for the morphine-induced place preference. Despite some procedural differences, these conclusions may be relevant for the interpretation of the data reported here. Basically, the expression of a sucrose-induced place preference in water-deprived animals may have depended upon a motivational state that facilitated approach behaviors. In fact, the observed conditioned place preference could be mediated by thirst as well as other variables (e.g., caloric content). Harris et al. (2000), for example, found that odor–calorie associations developed only when animals are hungry during training implying that motivation at the time of training influences the development of learned associations. Thus, attention should be paid to motivational elements of any place preference induction, as this procedure may be highly sensitive to motivational variables. Further work should also evaluate the possibility that the increased preference for the sucrose-paired side in Experiments 1 and 2 might have been mediated by food-seeking responses. These water-deprived

rats were likely to have consumed fewer calories during the day and thus, might find the sucrose-paired side more appealing than the water-paired side. Though food-seeking behavior might be partially mediating the sucrose-induced place preference, it remains that LPS did not disrupt the expression of a place preference but did disrupt sucrose intake and these data provide support for previous suggestions that LPS differentially affects various components of feeding (Cross-Mellor et al., 2000, 2003).

In summary, the expression of a sucrose-induced place preference appears to be sensitive to the motivational state of the animal at the time of testing. Regardless, data indicate that LPS and IL-1β disrupt sucrose consumption without affecting the expression of a sucrose-induced place preference. Thus, based on these data, it appears that conditioned and unconditioned behaviors may be differentially affected by cytokines and immune activation.

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References

Acquas E, Carboni E, Leone P, Di Chiara G. SCH 23390 blocks drug-conditioned place-preference and place-aversion: anhedonia (lack of reward) or apathy (lack of motivation) after dopamine receptor blockade? Psychopharmacology 1989;99:151–5.

Agmo A, Galvan A, Talamantes B. Reward and reinforcement produced by drinking sucrose: two processes that may depend on different neurotransmitters. Pharmacol Biochem Behav 1995;52:403–14.

Anisman H, Merali Z. Anhedonic and aniogenic effects of cytokine exposure. In: Dantzer R, Wollmann E, Yirmiya R, editors. Cytokines, stress, and depression: advances in experimental medicine and biology, vol. 461. New York: Kluwer Academic/Plenum; 1999. p. 199–233.

Anisman H, Kokkinidis L, Merali Z. Interleukin-2 decreases accumbal dopamine efflux and responding for rewarding lateral hypothalamic stimulation. Brain Res 1996;731:1–11.

Aubert A. Sickness and behavior in animals: a motivational perspective. Neurosci Biobehav Rev 1999;23:1029–36.

Aubert A, Dantzer R. The taste of sickness: lipopolysaccharide-induced finickiness in rats. Physiol Behav 2005;84:437–44.

Avitsur R, Pollak Y, Yirmiya R. Different receptor mechanisms mediate the effects of endotoxin and interleukin-1 on female sexual behavior. Brain Res 1997;773:149–61.

Beninger RJ, Hahn BL. Pimozide blocks establishment but not expression of amphetamine-produced environment-specific conditioning. Science 1983;220:1304–6.

Beninger RJ, Herz RS. Pimozide blocks establishment but not expression of cocaine-produced environment-specific conditioning. Life Sci 1986;38:1425–31.

Cardinal RN, Parkinson JA, Hall J, Everitt BJ. The contribution of the amygdala, nucleus accumbens, and prefrontal cortex to emotional and motivated behavior. Int Congr Ser 2003;1250:347–70.

Cohen J. Statistical power analysis for the behavioral sciences. 2nd edition. Hillsdale (NJ): Lawrence Earlbaum Associates; 1988.

Cross-Mellor SK, Kent WDT, Kavaliers M, Ossenkopp K-P. Examining the effects of lipopolysaccharide and cholecystokinin on water ingestion: comparing intake and palatability. Brain Res 2000;861:220–32.

Cross-Mellor SK, Roberts S, Kavaliers M, Ossenkopp K-P. Activation of immune system in rats with lipopolysaccharide reduces voluntary sucrose intake but not intraoral intake. Pharmacol Biochem Behav 2003;76:153–9.

Dantzer R, Aubert A, Bluthé RM, Gheusi G, Cremona S, Layé S, et al. Mechanisms of the behavioural effects of cytokines. Adv Exp Med Biol 1999;461:83–105.

Domjan M. The principles of learning and behavior. Fourth edition. Pacific Grove: Brooks/Cole Publishing Company; 1998.

Gibertini M, Newton C, Friedman K, Klein TW. Spatial learning and impairment in mice infected with *Legionella pneumophila* or administered endogenous interleukin-1β. Brain Behav Immun 1995;9:113–28.

Harris JA, Gorisse MC, Bailey GK, Westbrook RF. Motivational state regulates the content of learned flavor preferences. J Exp Psychol Anim Behav Process 2000;1:15–30.

Larson SJ, Dunn AJ. Behavioral effects of cytokines. Brain Behav Immun 2001;15:371–87.

Larson SJ, Romanoff RL, Dunn AJ, Glowa JR. Effects of interleukin-1β on food-maintained behavior in the mouse. Brain Behav Immun 2002;16:398–410.

McCarthy DO, Kluger MJ, Vander AJ. Suppression of food intake during infection: is interleukin-1 involved? Am J Clin Nutr 1985;42:1179–82.

McFarland K, Ettenberg A. Haloperidol does not affect motivational processes in an operant runway model of food-seeking behavior. Behav Neurosci 1998;112:630–5.

McFarland K, Ettenberg A. Haloperidol does not attenuate conditioned place preferences or locomotor activation produced by food- or heroin-predictive discriminative cues. Pharmacol Biochem Behav 1999;62:631–41.

Nakajima A, Yamada K, Nagai T, Uchiyama T, Miyamoto Y, Mamiya T, et al. Role of tumor necrosis factor-α in methamphetamine-induced drug dependence and neurotoxicity. J Neurosci 2004;24:2212–25.

Pugh CR, Fleshner M, Watkins LR, Maier SR, Rudy JW. The immune system and memory consolidation: a role for the cytokine IL-1β? Neurosci Biobehav Rev 2001;25:29–41.

Sahraei H, Fatemi SM, Pashaei-Rad S, Faghih-Monzavi Z, Salimi SH, Kamalinegad M. Effects of *Papaver rhoeas* extract on the acquisition and expression of morphine-induced conditioned place preference in mice. J Ethnopharmacol 2006;103:420–4.

Sparkman NL, Kohman RA, Garcia AK, Boehm GW. Peripheral lipopolysaccharide administration impairs two-way active avoidance conditioning in C57BL/6J mice. Physiol Behav 2005;85:278–88.

Spiteri T, Le Pape G, Agmo A. What is learned during place preference conditioning? A comparison of food- and morphine-induced reward. Psychobiology 2000;28:367–82.

Stefurak TL, van der Kooy D. Saccharin's rewarding, conditioned reinforcing, and memory improving properties: mediation by isomorphic or independent processes? Behav Neurosci 1992;106:125–39.

Suzuki T, Funada M, Sugano Y, Misawa M, Okutomi T, Soma G, et al. Effects of a lipopolysaccharide from *Pantoea agglomerans* on the cocaine-induced place preference. Life Sci 1994;54:75–80.

Williams BA, Dunn R. Preference for conditioned reinforcement. J Exp Anal Behav 1991;55:37–46.

Yirmiya R. Endotoxin produces a depressive-like episode in rats. Brain Res 1996;711:163–74.

Yirmiya R. Behavioral and psychological effects of immune activation: implications for 'depression due to a general medical condition'. Curr Opin Psychiatr 1997;10:470–6.