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Learning the morphine conditioned cue preference: Cue configuration determines effects of lesions

Norman M. White *, Sin Chee Chai, Selma Hamdani

Department of Psychology, McGill University, 1205 Dr Penfield Avenue, Montreal, Canada QC H3A 1B1

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Abstract

The morphine conditioned cue preference was investigated using two different apparatus configurations. In one configuration, with a clear Plexiglas partition separating the drug-paired and unpaired compartments, rats could see the cues in both compartments while in either one. In the other configuration, with an opaque wood partition separating the two compartments, rats could see the cues in only one compartment at a time. The experiment had three phases: a session of pre-exposure to the entire apparatus; four 2-day training trials during each of which rats received pairings of 5 mg/Kg morphine sulphate with one compartment and saline with the other (compartments and order counterbalanced), and a test session in which the undrugged rats moved freely between the compartments while the time spent in each was measured. Four groups of rats were trained using the opaque partition in all three phases. Normal rats and rats with amygdala or nucleus accumbens lesions exhibited preferences for their morphine-paired compartments; rats with fimbria-fornix lesions had no preferences. Four additional groups were trained using the clear partition during pre-exposure, the opaque partition during training and the clear partition during testing. Normal rats and rats with fimbria-fornix lesions exhibited preferences, rats with amygdala or nucleus accumbens lesions had no preferences. This interaction between lesioned structures and the apparatus configuration is accounted for by the idea that different types of learning produced the preference for morphine-paired cues in the two apparatus configurations. Each type was learned in a different memory system and so was impaired by different lesions. These findings contribute to understanding the nature of the learning processes that produce the morphine CCP.

Keywords: Morphine; Opiates; Conditioned cue preference; Memory systems; Reinforcement

1. Introduction

In the conditioned cue preference (CCP) paradigm (also called conditioned place preference) rats experience the effects of a reinforcer in the presence of a cue or set of cues. At a different time the rats are exposed to a different set of cues in the absence of the reinforcer. The effects of the reinforcer are then determined by giving the rat a choice between the two sets of cues in the absence of the reinforcer. A CCP exists if a rat spends more time in the presence of the reinforcer-paired than the control cues. This paradigm has been used to study the effects of various reinforcing events including, among many others, the consumption of food (Spyraki et al., 1982; White and McDonald, 1993; Everitt et al., 2003) and the administration of addictive drugs such as morphine (eg.,Mucha et al., 1982; Olmstead and Franklin, 1996; McBride et al., 1999). The CCPs produced by food and morphine have been demonstrated using a number of different apparatus configurations and training parameters (Carr et al., 1989; Schechter and Calcagnetti, 1993, 1998; Tzschentke, 1998).

It seems clear that a preference for reinforcer-paired cues in the absence of the reinforcer must be due to a learning process of some kind. Operationally, the CCP is a Pavlovian conditioning paradigm. Rats are injected with morphine and experience its consequences (UR) while being exposed to initially neutral cues (CS). The CS acquires the ability to elicit similar responses as CRs which result in behaviors that produce a preference for the drug-paired cues. The learning that produces the food CCP

* Corresponding author. Tel.: +1 514 398 6082; fax: +1 514 398 4896.
E-mail address: norman.white@mcgill.ca (N.M. White).

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has been described by various workers as either conditioned reward or conditioned reinforcement, an interpretation supported by the fact that it is impaired by lesions of the amygdala (McDonald and White, 1993; White and McDonald, 1993; Everitt et al., 2003), a structure thought to be critically involved in Pavlovian conditioning (LeDoux et al., 1990; Davis, 1992; Gaffan, 1992) and conditioned reward, or conditioned reinforcement (Weiskrantz, 1960; Jones and Mishkin, 1972; Everitt and Robbins, 2000; Everitt et al., 2003).

In contrast to these findings, Olmstead and Franklin (1994) have reported that amygdala lesions have no effect on the morphine CCP but that the behaviour is impaired by lesions of the fimbria-fornix (F-F). The present study began with experiments attempting to replicate Olmstead and Franklin's findings using a method originally developed to study how the food CCP is learned (White and McDonald, 1993). Those experiments used the distinct room cues visible from two arms on opposite sides of an 8-arm radial maze (Olton and Samuelson, 1976) as the food-paired and control cues. The arms were connected by the central platform of the maze. The food CCP in this situation is impaired by lesions of the amygdala, but not by lesions of F-F (White and McDonald, 1993). In Experiment 1 we tested the effects of amygdala and F-F lesions on the morphine CCP in this maze apparatus.

Although the results of this experiment did not agree with those of Olmstead and Franklin, a follow-up experiment in which the same rats were tested in a 3-compartment apparatus similar to the one used by those authors suggested that the discrepancy might be due to differences in the configuration of the apparatus used in the two experiments. This hypothesis was tested in Experiment 2 using two different configurations of a 3-compartment apparatus. In addition to lesions of amygdala and F-F, lesions of the nucleus accumbens (NAcc) were also tested in Experiment 2.

2. Experiment 1

2.1. Method

2.1.1. Subjects

Subjects were 32 male Long–Evans rats purchased from Charles River, Canada, weighing approximately 300–325 g at the start of the experiments. The rats were individually housed in a temperature-controlled room with the lights on from 7 am to 7 pm. All testing was done during the light period. The rats had free access to water and food throughout the experiment. All procedures used conformed to guidelines of the Canadian Council on Animal Care and were approved by the McGill University Faculty of Science Facility Animal Care Committee.

2.1.2. Surgery and histology

All rats undergoing surgery were anesthetized with sodium pentobarbital (60 mg/kg, ip). Bilateral lesions were made using standard stereotaxic techniques and coordinates based on the atlas of Paxinos and Watson (1998) measured in relation to bregma and the skull surface. Lesions were made using enamel-insulated Nichrome electrodes (0.25 mm in diameter).

Lesions aimed at the lateral nucleus of the amygdala (LNA) were made at coordinates 3.5 mm posterior to bregma; 5.5 mm lateral to the midline on both sides, and 8.5 mm below the skull surface (−3.5, 5.5, 8.5). Electrolytic current (1.5 mA, 20 s) was generated with a locally constructed lesion maker. The anode was attached to the electrode (1.0 mm exposed at the tip), the cathode was attached to an ear bar.

For F-F two lesions were made on each side of the brain. The coordinates were- 1.5, 0.8 and 2.2, 4.5. Radio-frequency current (6 mA, 30 s) was passed through electrodes with 0.8 mm exposed at the tip using a Grass Model 4 lesion maker. One lead was attached to the electrode, the other to the ear bar.

Sham-lesioned rats were anesthetized and placed into the stereotaxic apparatus. Their skulls were exposed but no holes were drilled and no electrodes were lowered into the brain.

After completion of behavioral testing the rats were deeply anesthetized with an injection of 30% chloral hydrate and perfused with 9% saline followed by 10% formol-saline solution. The brains were stored in 10% formol-saline for a week before sectioning. They were then frozen and cut into 30 um sections. Every fifth section through the lesion site was mounted on glass slides, stained with cresyl violet and examined microscopically. In each lesion group rats were prepared, tested and their brains examined until at least 8 rats with acceptable lesions (see Results) were available for analysis.

2.2. Apparatus

2.2.1. Radial maze

An eight-arm radial maze made of wood painted flat gray was used. The maze had an octagonal center platform 40 cm in diameter. Eight arms, 60 cm long and 9 cm wide, were attached to the eight sides of the platform. Rectangular wooden blocks ($35 \times 19 \times 8.5$ cm) were used to obstruct six of the eight arms. Two similar blocks had wooden panels (31×28.5 cm) attached to the end facing away from the center of the maze. These blocks were used to restrict the rats to their assigned drug-and saline-paired arms during the training trials. The maze was located in the center of a windowless, 2.9×2.9 m room that contained a variety of distal cues, including a small desk, some shelves, a vertical black plank in a corner and the door. A video camera was suspended from the ceiling above the center platform of the maze. All

observations were made on a monitor located in an adjacent room.

2.2.2. Three-compartment apparatus

The 3-compartment CCP apparatus was identical in size and shape to that used by Olmstead and Franklin (50). It consisted of a large box made of wood, except for the front wall, which was Plexiglas. The box was divided into two compartments of equal size ($45 \times 45 \times 30$ cm) by a wooden partition. One of the compartments was painted grey, the other was painted with vertical black and white stripes. Each compartment had a door (7×9 cm) in the rear wall, adjacent to the partition. The two doors were connected by a tunnel ($36 \times 18 \times 20$ cm) that protruded from the rear of the apparatus and straddled the partition between the two compartments. The doors could be closed by lowering a wooden panel.

The apparatus was situated in a brightly lit room about 60 cm from a one-way vision window, preventing the rats from seeing any of the cues in the room. The rats were observed from a darkened area on the other side of the window.

In contrast to the apparatus used by Olmstead and Franklin, in which the compartments contained different visual, tactual and olfactory cues, the floors in both compartments of the present apparatus were made of wood and covered with wood chips, so that only visual cues differentiated them. Since only visual cues differentiate arm locations on the radial maze, this aspect of the two CCP paradigms was similar.

In a pilot experiment groups of rats were treated according to the procedure of the present experiment using either the opaque or clear partition, except that they received no treatments of any kind. Although there were individual differences in unconditioned preference for the two compartments, the mean amounts of time spend in them on the test trial were nearly equal.

2.3. Procedure

Starting seven days after surgery all rats were handled daily for 4 days. Groups of 6–8 rats were put into a large handling box for 15 min. Each rat was picked up individually and handled for about 30 s 3 times during each session.

2.3.1. Radial maze

Each rat was assigned to 2 maze arm locations separated by at least 2 other arms. The maze was rotated one arm position to the left before the start of testing on each day of the experiment so that a different arm occupied each location every day. This made any small, unintended differences among the arms irrelevant to the location of the food. Arm location assignment was pseudorandom; each possible pair of arms separated by 2 other arms was used for at least one rat in each group. One of these arms was randomly designated as the morphine-paired arm, and the other was paired with a saline injection.

The procedure required 10 days. On day 1 all rats were pre-exposed to the maze. Each rat was placed individually on the center platform of the maze with its 2 assigned arms open and the other arms blocked. The rats were allowed to move freely on the maze for 10 min.

The training sessions were given on days 2 to 9. Over these 8 days each rat was confined on each of its 2 assigned arms on alternate days. In each group one half of the rats were placed on their morphine-paired arms on the even numbered days and on their saline-paired arms on the odd numbered days. The order was reversed for the other half of the rats in each group. Immediately before being placed on its morphine paired arm, each rat was given a subcutaneous injection of 5 mg/Kg morphine in 1 ml/Kg of physiological saline. Immediately before being placed on its saline-paired arm each rat received an injection of 1 ml/Kg of physiological saline. The rats remained on the arms for 30 min. Thus, each rat received a total of 4 two-day training trials. Each trial consisted of exposure to one arm under the influence of morphine and to another arm following a saline injection.

Day 10 was the test day. Each rat was placed on the center platform of the maze with its 2 assigned arms open (the other arms were blocked) and allowed to move freely on the maze for 20 min. The times at which a rat entered and exited each open arm were recorded and used to calculate the total time spent on each arm during the test. A rat was considered to be in an arm when its front feet crossed the threshold of the arm. A similar criterion was used to determine when a rat left an arm for the center platform.

2.3.2. Three-compartment apparatus

One week after the end of the maze experiment the rats in the LNA lesion group were retested in the 3-compartment apparatus. The procedure was similar to that used on the radial maze. The wood chips on the floors of the two compartments were changed before each trial for each rat. For pre-exposure, all rats were placed in the tunnel and allowed to explore the entire apparatus freely for 10 min. There were 4 two-day training trials. On one of the two days of each trial each rat received a morphine injection (5 mg/Kg) and was confined in one of the large compartments for 30 min. On the other day the rat received a saline injection and was confined in the other large compartment for 30 min. The drug-paired compartments and order of drug- and saline-pairing were counterbalanced. The test trial was given on the day after the last training trial. All rats were placed into the tunnel and allowed to explore the entire apparatus freely for 20 min. The times at which each rat entered and left the two large compartments were recorded and used to calculate the total time spent in each. A rat was considered to have entered a compartment when its front feet crossed the threshold; a similar criterion was used to decide when a rat left a compartment.

2.4. Results and discussion

Summary drawings of the histological material for the 8 rats in each group are shown in Fig. 1. The LNA lesions destroyed 80–95% of the anterior portion of the lateral nucleus and more than 90% of the posterior part of the lateral nucleus. Some rats had lesions which extended to adjacent basolateral and central amygdala, endopiriform nuclei and ventral hippocampus, partially damaging these structures. All F-F lesions completely transected the F-F at some anterior-posterior level. In all rats the lesions extended slightly into the dorsal hippocampus. The cortex and cingulum also sustained slight damage in many rats. There was a total of 8 rats with acceptable lesions both the LNA and F-F groups, and 8 rats in the sham-lesioned group.

The behavioral results are shown in Fig. 2. On the radial maze, preferences for the morphine-paired arm were observed in all groups except those that sustained lesions of the LNA. However, when the rats in the latter group were re-tested in the two compartment apparatus they exhibited a large CCP.

The data for the groups tested on the radial maze were analyzed using a two-way ANOVA with Groups as one factor and Arms as a repeated measure. There was a significant 2-way interaction between Groups and Arms [$F(2,21)=3.88$, $p<0.04$]. Pre-planned comparisons showed that the mean amounts of time spent in the morphine-and saline-paired Arms were significantly different for the Sham [$F(1,21)=12.45$, $p<0.01$} and F-F [$F(1,21)=5.62$, $p<0.03$] groups, but not for the LNA Group [$F(1,21)=0.09$].

Because of an inherent difference in the size of the preferences in the maze and two-compartment apparatus, the data for the retest of the LNA lesion group in the latter apparatus were analysed separately. A paired *t*-test showed that when tested in this apparatus the rats in this group had a significant preference for the morphine-paired compartment ($t(7)=6.60$, $p<.001$).

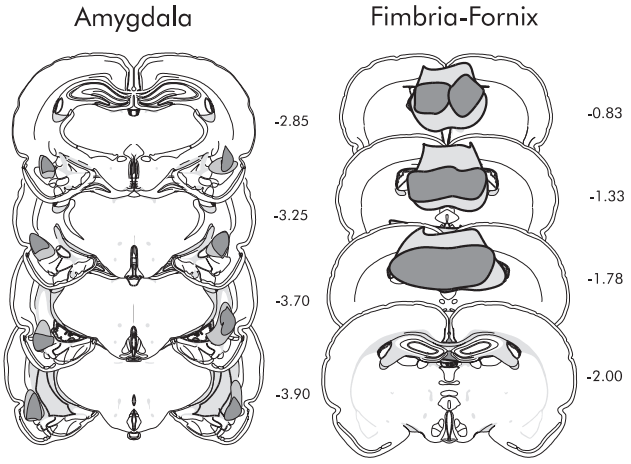

Fig. 1. Drawings of histological material from Experiment 1, based on atlas of Paxinos and Watson (54). Numbers on sections are mm anterior (+) or posterior (−) to bregma.

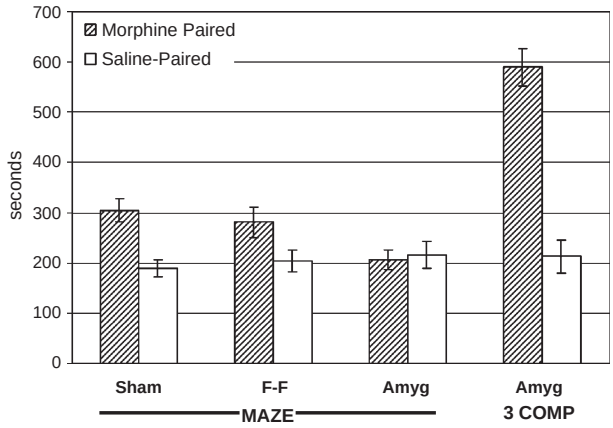

Fig. 2. CCP data from Experiment 1. The 3 leftmost pairs of bars show data for the radial maze; the pair on the right show data for the box apparatus (see text for descriptions). In each pair the shaded bar shows the time spent in the morphine-paired arm or compartment, the clear bar shows the time spent in the saline-paired arm or compartment. Values are means ± standard errors of the mean.

In Olmstead and Franklin's (1997) experiment F-F lesions impaired the morphine CCP in the 3-compartment apparatus but had no effect on the maze CCP in the present experiment. LNA lesions had no effect in Olmstead and Franklin's experiment, but impaired the CCP on the maze. However, the same rats with LNA lesions exhibited a large CCP in the 3-compartment apparatus. These differences suggest the possibility that the configuration of the apparatus may determine the effects of the lesions on the morphine CCP. This hypothesis was tested in Experiment 2.

3. Experiment 2

This experiment used a modified version of the 3-compartment apparatus from Experiment 1 to examine the influence of apparatus configuration on morphine CCP learning. The apparatus was identical except that the partition separating the two compartments was removable. Two different partitions were used. An opaque partition prevented a rat in one compartment from seeing the cues in the other compartment. Replacing the opaque partition with a clear Plexiglas partition allowed the rats to see the cues in both compartments while in either one.

During the training trials on the radial maze the rats are confined to the ends of the drug-paired and unpaired arms with wooden panels that restrict their view of the environmental cues so that they see different sets of cues from each arm. When they are on one arm they cannot see the cues that are visible from the other arm. This condition is similar to that produced by the opaque partition in the 3-compartment apparatus. During pre-exposure and testing on the radial maze both arms are open and the rat can move freely between them and the central platform. They can see most of the room cues (including those visible

from both arms) from anywhere within this space. This condition is similar to that produced by the use of the clear partition in the 3-compartment apparatus.

Two configurations of the 3-compartment apparatus were used in the present experiment. One was identical to that used by Olmstead and Franklin (1997): the opaque partition was used in all three phases (pre-exposure, training, testing) of the procedure. This was the OOO condition. The other replicated the conditions during each of the three phases of the separated arm CCP procedure on the radial maze: the clear partition was used during the pre-exposure and test trials and the opaque partition was used during the training trials. This was the COC condition.

The effects of LNA and F-F lesions on the morphine CCP were tested in these two conditions. There are also conflicting reports concerning the effects of nucleus accumbens (NAcc) lesions on the morphine CCP. Both electrolytic (Kelsey et al., 1989) and dopamine-specific (Shippenberg et al., 1993) lesions of NAcc have been shown to impair the morphine CCP. In both of these studies, the rats were tested in situations where they could see both the drug-paired and neutral cues during the test trial. In contrast, Olmstead and Franklin (1996, 1997) found that NAcc lesions made with NMDA or 6-OHDA had no effect on the morphine CCP using the OOO procedure, in which the rats could see the cues in only one compartment at a time. This suggests that the apparatus configuration may also determine the effects of NAcc lesions on the morphine CCP, and this hypothesis was also tested in the present experiment.

3.1. Method

3.1.1. Subjects

Subjects were 85 rats identical to those used in Experiment 1.

3.1.2. Surgery and histology

The procedure for the LNA and F-F lesions was identical to that described in Experiment 1. Electrolytic lesions (4 mA, 20 s) of NAcc (NAcc) were made at coordinates (1.8, 1.7,−7.9) using an electrode with 1 mm exposed at the tip, as described in Experiment 1. All brains with lesions were prepared for histological analysis as described in Experiment 1. In each lesion group for each condition, additional rats were prepared and tested until a minimum of 8 with acceptable lesions were available. When this procedure produced more than 8 rats with acceptable lesions in any group, all of them were included in the statistical analysis. Several sham-lesioned rats were run together with each cohort of lesioned rats and all of these were included in the analysis.

3.1.3. Apparatus

Except for the interchangeable wood and Plexiglas partitions between the two large compartments, the apparatus was identical in size, shape and visual cues to the 3-compartment apparatus described in Experiment 1.

3.1.4. Procedure

The general experimental procedure was identical to that described for Experiment 1. There were two different CCP conditions. In the O-O-O condition the opaque partition was used to separate the paired and unpaired compartments in all phases of the experiment. In the C-O-C condition the clear partition was used during pre-exposure (10 min) and testing (20 min) and the opaque partition was used during the training trials (4-two-day trials, 30 min each day).

3.2. Results and discussion

Summary drawings of the histological material are shown in Fig. 3. The LNA and F-F lesions were very

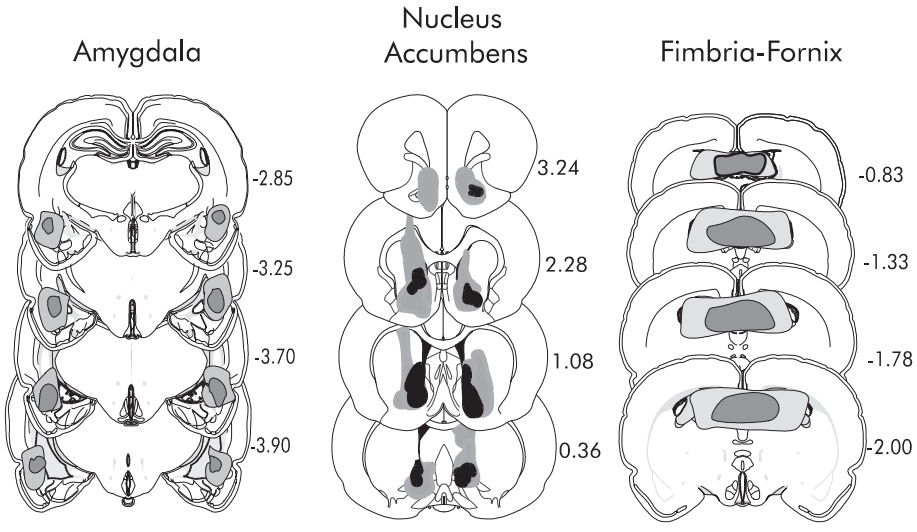

Fig. 3. Drawings of histological material from Experiment 2, based on atlas of Paxinos and Watson (54). Numbers on sections are mm anterior (+) or posterior (−) to bregma.

similar to those described for Experiment 1. The NAcc lesions destroyed the entire structure in all rats. In addition, damage to dorsal striatum and areas lateral to NAcc occurred in a few rats. As there were no behavioral effects of this extra damage in any individual, these rats were retained for analysis of the behavioral data. The final Ns for each group were: OOO: Sham=16, NAcc=8, LNA=8, F-F=8; COC: Sham=16, NAcc=9, LNA=12, F-F=8.

The behavioral results are shown in Fig. 4. In the OOO condition morphine CCPs were observed in the Sham, NAcc and LNA groups, but not in the F-F group. This replicates the findings of Olmstead and Franklin (1996, 1997). The opposite pattern of effects was observed in the COC condition: CCPs were observed in the Sham and LNA groups, but not in the NAcc or LNA groups.

These results were analyzed using a three-way ANOVA, with Condition and Groups as main effects and Compartment as a repeated measure. There was a significant 3-way interaction [$F(3,77)=3.97$, $p<0.02$], and significant main effects of Condition [$F(1,77)=10.13$, $p<0.01$] and Group [$F(3,77)=22.16$, $p<0.001$]. For the OOO condition, pre-planned comparisons showed that the amounts of time spent in the morphine-and saline-paired arms differed significantly for the Sham [$F(1,77)=65.95$, $p<0.001$] , NAcc [$F(1,77)=16.04$, $p<0.001$] and LNA [$F(1,77)=13.13$, $p<0.001$] groups, but not for the F-F group [$F(1,77)=2.56$]. For the COC condition, there were significant preferences for the Sham [$F(1,77)=54.38$, $p<0.001$], and F-F [$F(1,77)=9.16$, $p<0.01$] groups, but not for the NAcc [$F(1,77)=0.02$] or LNA [$F(1,77)=0.21$] groups.

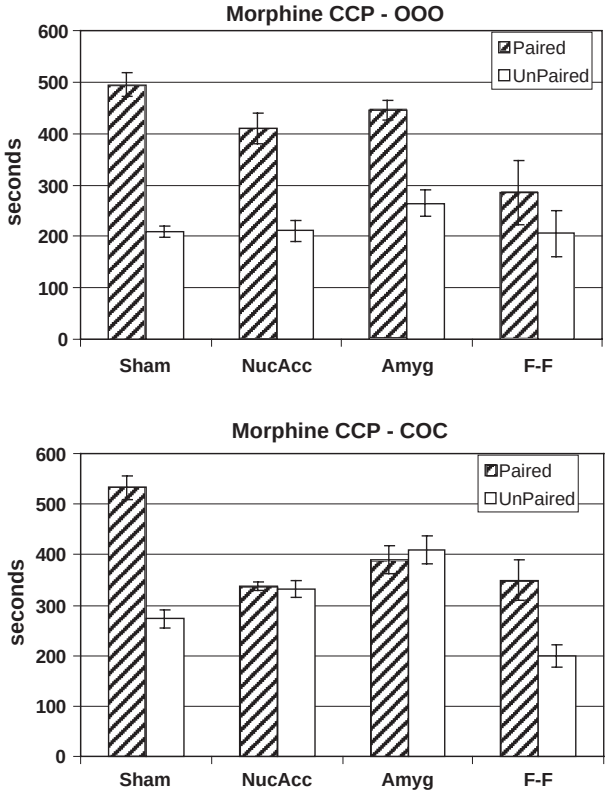

Fig. 4. CCP data from Experiment 2. The top graph shows the effects of lesions of the nucleus accumbens (NucAcc), amygdala (Amyg) and fimbria-fornix (F-F) on the CCP in the box apparatus with the use of an opaque partition separating the morphine-paired and unpaired compartments in all three phases of the experiment (OOO). The bottom graph shows the effects of the same three lesions with the use of the clear partition during the pre-exposure and testing phases and the opaque partition during the training phase. In each pair the shaded bar shows the time spent in the morphine-paired arm or compartment, the clear bar shows the time spent in the saline-paired arm or compartment. Values are means±standard errors of the mean.

These results are consistent with the hypothesis that cue visibility during unreinforced pre-exposure or testing (or both) influences the effects of LNA, NAcc and F-F lesions on the morphine CCP. The use of counterbalancing – within each group equal numbers of rats were randomly assigned to receive morphine in both compartments – means that the effects observed cannot be attributed to biased initial preferences for the cues in the compartments or to differences in the tendency for those cues to become associated with the effects of morphine. Furthermore, the use of two different partitions in the same apparatus means that the differences in the lesion effects cannot be attributed to differences in the cues that were associated with the drug effects or in the behaviour required to exhibit a preference in the two conditions.

4. General discussion

CCPs in general and the morphine CCP in particular have been observed using a variety of different apparatus configurations (Carr et al., 1989; Tzschentke, 1998). The present experiments are the first to compare different configurations directly and to show that different brain systems mediate the CCPs observed in each case.

Since the preferences observed on the test trial of the CCP paradigm occurred in the absence of the drug, they must have been due to a memory of one or more effects produced by morphine when it was present during the training trials. For this reason, an interpretation of the present results in terms of how learning new behaviours is mediated in the brain may be a useful way to understand the findings. Considerable converging evidence suggests that there are different types of learning and memory, and that these types are mediated in different brain systems (Tolman, 1949; Scoville and Milner, 1957; Milner et al., 1968; Hirsh, 1974; O'Keefe and Nadel, 1978; Mishkin et al., 1984; Milner, 1985; White and McDonald, 2002; White, 2004). Applying this idea to the present findings suggests that, in normal rats, the CCP observed in the OOO condition reflects learning that occurred in a memory system that includes F-F, but not amygdala or NAcc; and that the CCP observed in the COC condition reflects learning that occurred in a system that includes the amygdala and NAcc, but not F-F. The

multiple memory system hypothesis leads to the suggestion that two different kinds of learning involving the effects of morphine and the cues in the compartments occurred simultaneously and in parallel during the training trials. One of these was mediated in a neural system that includes F-F, the other in a neural system that includes amygdala and NAcc.

Both forms of learning would have occurred in the control rats (with normal brains), so they exhibited CCPs in both conditions. However, F-F lesions prevented acquisition or expression of one of these forms of learning. This was apparent in rats tested with the opaque partition, presumably because the kind of learning mediated by the intact amygdala and NAcc could not produce a CCP in this condition. Therefore, the morphine CCP observed with the opaque partition requires F-F-mediated learning. Conversely, amygdala and NAcc lesions prevented acquisition or expression of a different form of learning. This was apparent with the clear partition, presumably because the type of learning mediated by the intact F-F could not produce a CCP in that condition. Therefore, the morphine CCP observed with the clear partition requires a form of learning mediated by amygdala and NAcc.

Evidence about the kinds of learning and memory mediated by these neural systems suggests an explanation for the observed lesion effects that focuses on the learning that occurs during the training trials and on expression of the information learned during the test trial.

4.1. Learning in the OOO condition

CCP expression with the opaque partition was impaired by F-F lesions. The memory system that includes F-F and hippocampus (74) acquires representations of relationships among cues (O'Keefe and Nadel, 1978; O'Keefe, 1990; Eichenbaum, 1992; Muller et al., 1996; Rolls, 1996), one function of which is thought to be the formation of spatial maps. Although hippocampal function is sometimes referred to as cognitive learning, or the acquisition of "knowledge", there is evidence that the hippocampus also responds to internal states, representing relationships among cues resulting from these states and concurrent external cues (Hirsh, 1974; Hirsh et al., 1978; Davidson et al., 1992; Davidson and Jarrard, 1993; Tracy et al., 2001; Kennedy and Shapiro, 2004; Moita et al., 2004). Accordingly, the hippocampus is capable of representing information about the relationships among internal affective states produced by drugs and cues in the situation where these states are experienced. Information about these relationships would result in behaviours guided by the drug-produced internal states.

Note that the experience of an affective state such as reward, by itself, has no influence on behavior. It can have such an influence only when information has been learned about its relationship to the cues in the situation in which it occurs. That is, an individual must learn how to interact with the cues in its environment (ie, what to do) to produce and maintain rewarding states in order for them to have any observable effect on behavior.

Impairment of the OOO CCP by F-F lesions suggests that hippocampus-mediated learning about the relationship between the rewarding effects of morphine and the cues in the drug-paired compartment produced the CCP in this condition. As pointed out in the Introduction, operationally, the CCP is a Palvovian paradigm. However, this does not mean that this is the only kind of learning that can occur in this situation. The pattern of lesion effects suggests that test trial behavior was also influenced by hippocampus-based learning about reward.

4.2. Learning in the COC condition

Amygdala and NAcc lesions both impaired the CCP in the COC condition. The memory system that includes the amygdala (74) is thought to mediate Pavlovian conditioning (Weiskrantz, 1960; Jones and Mishkin, 1972; Everitt et al., 2003), and is closely associated with NAcc in producing behaviours attributed by various workers to conditioned reward or reinforcement (Everitt et al., 1989; Cador et al., 1989; Everitt, 1990; Everitt et al., 1999, 2003), or incentive salience (Robinson and Berridge, 1993; Salamone et al., 2005). If the COC CCP was due to classical conditioning, as suggested by the fact that it was impaired by amygdala lesions, we can ask what unconditioned effects of morphine (the reinforcer) could have become conditioned responses that produced the CCP.

4.2.1. Conditioned approach responses

When some reinforcers are encountered they elicit approach responses as URs (Maier and Schnierla, 1964; Glickman and Schiff, 1967; Bindra, 1969; Stellar et al., 1979; White and Milner, 1992; Timberlake, 1993). These URs may be subject to conditioning. If so, they could be elicited as CRs by visible CSs such as those in the drug-paired compartment.

This kind of conditioned approach response may be related to the phenomenon of autoshaping (Brown and Jenkins, 1968; Jenkins and Moore, 1973; Browne, 1976; Leslie et al., 1979), which can occur when rats are presented with uncorrelated food (US) and light (CS) cues. Rats acquire an approach response to the cue even though this response was never explicitly reinforced, and the response is maintained even when it is explicitly not reinforced (omission training). As described by Everitt, Robbins and colleagues (Cardinal et al., 2002a; Everitt et al., 2003), autoshaping depends on an intact amygdala and NAcc (Parkinson et al., 2000; Cardinal et al., 2002b). Although there is no evidence that morphine or any other drug can produce autoshaped responses, if this form of learning does occur it could be elicited by conditioned CSs such as the cues in the drug-paired compartment.

4.2.2. Conditioned reward

If morphine produces unconditioned rewarding effects, these can presumably become conditioned, and would be elicited as conditioned reward by the cues in the drug-paired compartment. However, just as unconditioned reward itself cannot directly influence behavior, conditioned reward also requires some form of hippocampus-based instrumental learning to produce behaviour that results in a CCP. Although this form of learning may occur in normal rats, it would be impaired by lesions to structures that are part of the hippocampus system, including F-F. Therefore, the present pattern of lesion effects suggests that conditioned reward does not contribute to the COC CCP.

In summary, impairment of the COC CCP by amygdala and NAcc lesions suggests that it was produced by a conditioned approach or autoshaped response. The lesions in the present experiment were not intended to differentiate among subsystems within the amygdala or nucleus accumbens. However, it can be noted that there is evidence suggesting that the basolateral nucleus of the amygdala may mediate conditioned responses that are influenced by the current motivational state of an animal, while the more medial nuclei may mediate more specific conditioned responses (Cardinal et al., 2002a; Holland and Gallagher, 2004). The lesions in the present experiment were centered on the lateral nucleus, which may be involved in both kinds of conditioned responses (Rainnie et al., 1991; LeDoux and Farb, 1991). Most of them partially damaged the basolateral nucleus and some extended slightly into the medial nuclei, so they do not provide any information about possible functional differences between these groups of nuclei. There is also some evidence that the core and shell compartments of NAcc (Voorn et al., 1989; Heimer et al., 1991; Nowend et al., 2001) have different functions (Deutch and Cameron, 1992; Corbit et al., 2001; Nowend et al., 2001; Di Chiara, 2002; Di Chiara et al., 2004). However, the present NAcc lesions consistently damaged both of these compartments almost completely, and so do not provide any new information about possible functional differences between them.

4.3. Expression of parallel learning with clear and opaque partitions

On the test trial with the clear partition the rats could see the conditioned cues from anywhere in the apparatus. If these cues elicited a conditioned orienting/approach response this could have increased the probability that the rats would enter and remain in the drug-paired compartment, leading to the observed preference. This hypothesis is consistent with the impairment of the COC CCP by lesions of the amygdala and NAcc. Since the hippocampus system is not involved in conditioned approach responding, rats with F-F lesions exhibited CCPs with the clear partition.

During the test trial with the opaque partition, rats could not see the cues in the drug-paired compartment unless they were already in it. In this case, a memory of the relationship of the drug-paired cues to the rewarding effects of morphine may have influenced the rat to move to that compartment and to spend more time there, resulting in a CCP. This form of learning would be hippocampus- based, consistent with the fact that the opaque partition CCP was impaired by F-F lesions. Conditioned approach responses, which were presumably intact in the rats with F-F lesions could not produce a CCP in this condition because the rats could not see the cues in the paired compartment unless they were already in it. Since the amygdala system is not involved in learning about the relationship between internal rewarding and external cues, rats with amygdala or NAcc lesions exhibited CCPs with the opaque partition.

4.4. Morphine's discriminative stimulus

Van der Kooy and co-workers (van der Kooy et al., 1982; Mucha et al., 1982; Mucha and Iversen, 1984) demonstrated the morphine CCP used an apparatus equivalent to the present COC configuration to investigate morphine's discriminative stimulus (Martin et al., 1990). Rats were injected with morphine, given a saccharin solution to drink and then injected with LiCl. On alternate days saline was substituted for both morphine and LiCl. Saccharin consumption was reduced on drug days (a LiCL-produced conditioned taste aversion) compared to saline control days, leading to the inference that the rats were able to use some internal effect of morphine (its stimulus property) to "predict" when consumption of the saccharin solution would have aversive consequences.

Central injections of morphine into the parabrachial nucleus, but not a number of other brain structures duplicated this effect of peripheral injections (Jaeger and van der Kooy, 1993) suggesting that an effect of the drug at this site produces a similar discriminative stimulus. However, parabrachial injections of morphine failed to produce a CCP (Jaeger and van der Kooy, 1996). In contrast, morphine injections into the ventral tegmental area produced a CCP, but not a discriminative stimulus (Jaeger and van der Kooy, 1996). The authors concluded that the discriminative stimulus and reinforcing (motivational) properties of morphine are independent, and that the discriminative stimulus is probably morphine's "rewarding" effects. Their experiments suggest that this discriminative stimulus is not the basis of the CCP, but that it may be produced by activation of dopaminergic cells in ventral tegmental area leading to dopamine release in the NAcc. This results in the attribution of "incentive salience" to the drug-paired cues leading to a tendency to approach and interact with them (Robinson and Berridge, 1993; Salamone et al., 2005).

This conclusion is congruent with the interpretation of the present findings in terms of independent learning by different memory systems. In the COC configuration the CCP was attributed to a conditioned orienting/approach response mediated by a neural system including NAcc and

amygdala. In the OOO configuration the CCP was attributed to learning about the rewarding effect of morphine. Jaeger and van der Kooy's conclusion that morphine injected into the parabrachial nucleus produces a rewarding stimulus leads to the prediction that these injections would produce a CCP in the OOO condition.

4.5. Effects of pre-exposure

During the pre-exposure phase of the procedure the rats explored the apparatus with no reinforcers present. Although learning occurs during this kind of activity it can be detected only when a reinforcer is introduced and the rats acquire a new behavior. Unreinforced pre-exposure facilitates subsequent spatial learning, a phenomenon known as latent learning (Blodgett, 1929; Tolman and Honzik, 1930; Kimble and BreMiller, 1981), but retards subsequent Pavlovian conditioning, a phenomenon known as latent inhibition (Lubow, 1973, 1975; Hall and Pearce, 1979). These observations suggest that the major determinant of the effect of unreinforced pre-exposure is the kind of learning that follows it. Even if the normal rats in the present experiment acquired different representations of the cues in the two compartments during pre-exposure with the opaque and clear partitions, the fact that the same partition was used for the training trials in both the OOO and COC conditions makes it unlikely that these representations had different effects on the drug-related learning that occurred during training.

The lesions in the present experiment were made before the pre-exposure session, raising the possibility that they could have affected the learning process that results in either latent learning or latent inhibition, and that the resulting differences in information acquired during pre-exposure could in turn have affected what was learned during the training trials in different ways. Lesions of F-F (Chai and White, 2004) impair spatial latent learning but have no effect on non-spatial latent (incidental) learning (Gaffan et al., 2003) or latent inhibition when rats are pre-exposed to a tone before it is paired with shock (Weiner et al., 1998; Pouzet et al., 1999). Since the hypothesized learning in the OOO configuration was non-spatial, it follows that it is unlikely that F-F lesions affected what was learned during pre-exposure, or that subsequent morphine CCP learning was differentially affected in the rats with F-F lesions.

There is no evidence latent learning affects either conditioned responses in general, or the conditioned approach responding thought to produce the COC CCP. However, conditioned responding is affected by latent inhibition. Latent inhibition is not affected by lesions of the amygdala (Weiner et al., 1995) but NAcc lesions impair or eliminate it (Tai et al., 1995; Weiner et al., 1996). Accordingly, latent inhibition of the morphine conditioned approach response during the training trials could have occurred in normal rats, but been attenuated or eliminated in the rats with NAcc lesions. This hypothesis predicts that the COC CCP should have been larger in the rats with NAcc lesions than in the sham-lesioned rats. As this prediction is contrary to the observed results, it seems unlikely that morphine CCP learning in the COC condition was affected by latent inhibition due to pre-exposure to the subsequently conditioned cues.

Although these considerations suggest that an effect of the lesions on learning during pre-exposure was unlikely, it should be clear that a definitive answer to this question can only be provided by experiments that compare morphine CCP learning in normal and lesioned rats that have been pre-exposed and not pre-exposed.

4.6. Conclusion

The present findings suggest that morphine's effects are produced by two different learning processes, each interacting with a different reinforcing effect of the drug. According to this analysis, morphine has a rewarding effect that affects behavior through hippocampus-based learning about the situation in which this effect was experienced. Morphine also appears to promote an amygdala and nucleus accumbens-based conditioned approach behaviour to drug-paired cues. The findings suggest that both forms of learning can influence behaviour simultaneously. These influences can be observed separately in special situations such as the OOO and COC paradigms in the CCP learning situation.

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