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Detour behavior changes associated with prenatal morphine exposure in 11-day-old chicks

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ABSTRACT

The central nervous system exhibits remarkable plasticity in early life. Prenatal morphine exposure may induce adverse behavioral effects on the neonate and the developing offspring. In the present study, we investigated the effect of prenatal morphine exposure (daily from embryonic days 12–16, 20 mg/kg) on 11-day-old chicks using two forms of spatial paradigms: one trial detour behavior task in which animals must bypass an obstacle to reach the desired goal without any training and detour learning task which required several trials of training to reach the detour criterion.

The results showed that, on the condition that chicks could successfully detour in the first trial, morphine exposed chicks exhibited longer detour latency to finish the task, coupled by a preference for turning right versus turning left. In contrast, no significant difference in learning and memory was found in detour learning task between morphine exposed chicks and saline chicks. These findings suggest specific behavioral changes associated with prenatal exposure to opioids during mid to late gestation, also raise attention to the possible health hazard from pregnancy drug use in everyday life.

1. Introduction

Drug abuse during pregnancy has been a major public health issue because of the concern about possible adverse behavioral effects on the neonate and the developing child. Collected findings from published studies to date suggest devastating effects on the development of infants (Lester et al., 2002; Metosky and Vondra, 1995) and even long-term neurobehavioral and/or cognitive changes during postnatal maturation (Pulsifer et al., 2004; van Baar and de Graaff, 1994; Wetherington et al., 1996; Zuckerman and Bresnahan, 1991).

The endogenous opioids and opioid receptors are present in a tonic balance in the central nervous system (CNS) during development, which is particularly susceptible to administration of opioid agonists and antagonists. The highest concentrations of opioid receptors in rat brain are present in several brain areas including the limbic system, thalamus, striatum, hypothalamus, midbrain and spinal cord (Mansour et al., 1987). This wide anatomical distribution of opiate receptors suggests that opiates may influence a large variety of functional pathways. Relevant evidence indicates that prenatal morphine exposure can produce long-term changes in the opiate system of the adult offspring (Vathy, 2002; Vathy et al., 2003), affect analgesia and pain perception (Chiou et al., 2003), social behavior (Hol et al., 1996; Niesink et al., 1996), and even attention and stress response (Hamilton et al., 2005).

Animal studies have shown that learning and memory can be impaired by prenatal administration of opiates (Schrott et al., 2008; Slamberova et al., 2005, 2001). Maternal exposure to morphine reduces synaptic plasticity in CA1 pyramidal neurons of the hippocampus in rat offspring, decreases phosphorylation of cyclic adenosine monophosphate- responsive element-binding protein (CREBSerine-133), an important transcription factor underlying learning and memory (Yang et al., 2003). A recent study (Sarkaki et al., 2008) has demonstrated that parental morphine addiction reduced hippocampal long-term potentiation (LTP) in offspring. While the role of the hippocampus in spatial learning has been well documented in many species of birds and mammals (Colombo and Broadbent, 2000), we hypothesized that prenatal morphine exposure may also affect spatial recognition and memory in chicks.

The in ovo development of egg in the absence of maternal factors makes chicken an excellent developmental animal model, allowing us to determine the specific biological contributions of prenatal morphine administration on neurodevelopmental

Abbreviations: CNS, central nervous system; IMM, intermediate medial mesopallium; LTP, hippocampal long-term potentiation; MSt, medial striatum; NE, norepinephrine.

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outcome while controlling for variables that usually encountered in clinical studies, such as altered nutrition in pregnancy and suboptimal rearing environment of the offspring. Accordingly, observations on the direct neurodevelopmental effects of the agent of interest are facilitated. What is more, as a precocial bird, chicks learn rapidly from the moment they hatch, need actively to explore and learn about their rearing environments, Thus, the young chick has been considered a good model for memory studies (Rose, 2000).

Detour behavior refers to the ability of an animal to find a route to a desired goal point pasting some obstacles. The study originated with Köhler (1925) and has been used to test spatial learning and memory (Regolin and Rose, 1999). Previous study has demonstrated the detour ability of chicks (Regolin et al., 1995). There are two forms of detour: one-trial detour test in which chicks could solve the detour problem within the first trial and detour learning task which required repeated trials of learning to accomplish the detour problem. Although the detour behaviors seem similar in the two task, the cognitive processes engaged in are distinct: one-trial detour test represents the ability to reason that objects are separate entities that continue to exist when they are no longer available to direct perception; detour learning represents the ability to learn and memorize the correct route and the reinforcement after following that route (Wynne and Leguet, 2004). The purpose of the present study was to investigate the potential influence of prenatal mid to late gestation morphine exposure on young chick's spatial behavior using both detour paradigms.

2. Experimental procedures

2.1. General methods

2.1.1. Subjects and their treatment

Lohmann brown eggs on embryonic day 10 (E 10) were obtained from a local commercial hatchery (suburban area of Kunming, Yunnan, PR China), and were incubated in a standard incubator with conditions maintained at 37.8 °C and 50–60% relative humidity. Eggs on E12 were weighed, numbered and randomly assigned to 2 groups: (1) embryonic eggs injected with morphine (20 mg/kg), the dose was chosen because it could induce morphine tolerance and dependence in chick embryos (Newby-Schmidt and Norton, 1981); (2) embryonic eggs injected with 0.9% sterile physiological saline (2 ml/kg). An ampoule of morphine hydrochloride (10 mg/ml, Shenyang Pharmaceutical Factory, Shenyang, PR China) was used daily from E12 to E16 according to our previous study (Che et al., 2005).

2.1.2. Postnatal rearing conditions

Chicks hatched inside the incubator at E20 or E21 and were left to dry completely (up to 12 h) before they were removed and weighted. After that different groups of chicks were reared in separate rectangular cages (50 cm × 25 cm, with 25 cm high walls) at controlled temperature 30.8–35.8 °C, with food and water available ad libitum. The domestic chicks were exposed to a photoperiod of 12-h light and 12-h dark cycle. Chicks of each group were individually marked with stock markers for identification. Experiments were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee of Kunming Institute of Zoolog, Chinese Academy of Sciences.

2.2. Experiment 1

2.2.1. Apparatus

The training arena (shown in Fig. 1) was a large wooden rectangular box (40 cm wide × 40 cm deep × 30 cm high). Within the arena, a H-shaped barrier was placed to produce an inner corridor 22 cm long and 12 cm wide, and two external symmetrical side corridors 14 cm each wide. The barrier was made of two wooden walls and a Plexiglas wall. On the opposite, 5 cm from the closest side of the barrier, a small cage (10 cm × 10 cm × 20 cm) was positioned adjacent to the outer wall, where we placed a group of three chicks (not used as subjects) just before each experimental session and scattered with a small amount of moistened chick food, to provide an attractive goal object for the test chick. The side of the cage, facing the central of the arena was transparent. Under these conditions the opportunity for access to food and brood mates was appropriate stimulus for reinforcing the detour response, resulting in shorter latencies as subjects learn to detour. There were no visual or acoustic cues external to the apparatus that the test chick could use for orienting itself during the task. The arena was placed in a darkened room. The only light in the experimental room was a 40-W lamp situated just above the centre of the arena itself. The experimenter remained out of sight to the chicks throughout the training protocol.

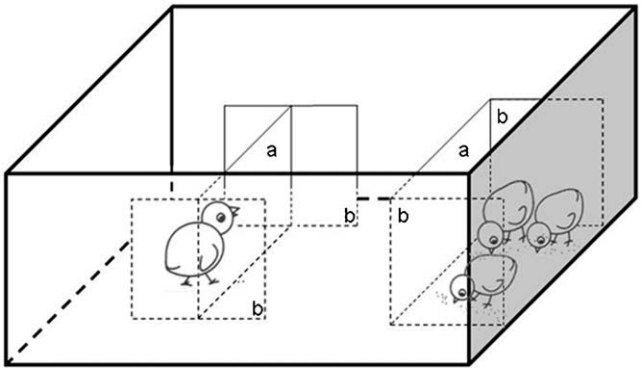

Fig. 1. The schematic diagram of detour apparatus used in experiment 1. The tested chick is isolated from a social group by a H-shaped barrier. In order to approach the desired goal, the isolated subject has to turn around, detouring from either left or right side. The letter "a" refers to: transparent Plexiglas wall, "b": opaque wall.

2.2.2. Procedures

On day 11, we picked up each chick in turn from its home cage and placed it into the arena, inside the barrier, facing the small cage. The isolated chick was strongly attracted by the group of conspecifics, but to approach them it had to turn around and walk towards the open end of the barrier, then exit by turning either right or left. In so doing, visual (although not acoustic) contact with the goal chicks was temporarily lost, until the test chick reached one of the outside corners of the H-shaped barrier. The time taken by each chick to reach the cage from the starting position and the direction of detour were recorded. Besides the latency of the test chick to exhibit typical attraction in the novel environment on the first trial was recorded. A cutoff time of 300 s was used. Once the chick had passed around the barrier we left it near the goal chicks for about 10 s before returning it to its home cage. At retest we repeated this procedure and recorded how long each chick took to make a detour around the barrier, at 30 min, 2 h, 12h, 24 h and 48 h after initial training.

2.2.3. Data analysis

All data were analyzed using a statistical package for social sciences (SPSS 10.0). Data were expressed as mean ± standard error of the mean (S.E.M.). Statistical significance was set at the probability level of $p < 0.05$. The times needed to solve the task were analyzed with two-way repeated-measures ANOVA, using treatment as a between-subjects factor and trial as a within-subjects factor. Further analysis was performed with Student t-test when appropriate.

Lateral asymmetries in the direction of detour responses were calculated using the index (Vallortigara et al., 1999a): (detour to the right–detour to the left)/(detour to the right + detour to the left) × 100. 'Detour to the right (left)' represented the number of times each chick turn around the barrier on the right (left) side during the six consecutive trials. These indices were then analyzed by ANOVA using treatment as a between-subjects factor. Significant departures from chance level (0%) were estimated by one-sample two-tailed t-tests.

2.3. Experiment 2

2.3.1. Apparatus and procedure

The arena (see Fig. 4) was a slightly modified version of the one used in the previous experiment. A smaller rectangular space (40 cm × 20 cm × 30 cm) contained the same H-shaped barrier, which separated the arena into two compartments (social and isolation sides). Four domestic chicks were randomly selected from the community brooder and placed on the social side of the detour apparatus, where we scattered with a small amount of moistened domestic chick food. Subjects were allowed access to the food and social reinforcement for 30 s, after which one was selected and placed in the center of the isolation side of the apparatus. This subject was allowed 180 s to face away from the reinforcing complex and detour through the open tunnel. If no detour response was made during this time, its latency was recorded as the maximum 180 s and the subject was gently guided through one fixed tunnel with a wooden ruler, terminating the trial. This sequence was repeated with the next subject until each of the four domestic chicks had received one trial. Detour learning task started on post hatch day 11 and is performed twice a day from post hatch day 11 to post hatch day 13. After 3 days of testing each animal received six trials. Before each detour learning test, the animals were deprived of food for 12 h.

2.3.2. Data analysis

The times needed to solve the task were analyzed with two-way repeated-measures ANOVA, using treatment as a between-subjects factor and trial as a within-subjects factor. Difference in the number of trails required for each chick to learn detour in two groups was analyzed with Student t-test. Data were expressed as mean ± S.E.M.

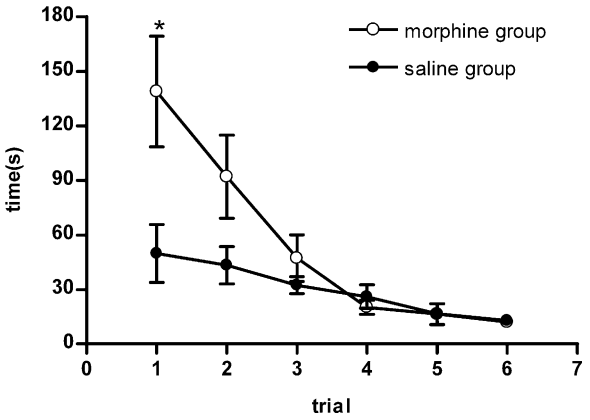

Fig. 2. The effect of prenatal morphine exposure on one-trial detour behavior. Each point represents the times (mean + S.E.M.) taken by chicks to make a detour around the barrier on the first trial and at successive retests. (*) significant difference between morphine exposed ($N = 10$) and saline exposed ($N = 11$) chicks, $p < 0.05$ (t-test).

3. Results

3.1. Experiment 1: effect of prenatal morphine exposure on one-trial detour behavior in chicks

3.1.1. Detour latency

Of the 21chicks used in the experiment, all solved the task during the first trial. Time taken by prenatal morphine exposed chicks ($N = 10$) and prenatal saline exposed chicks ($N = 11$) to finish detour were shown in Fig. 2. The two-way repeated-measures ANOVA analysis showed that there was a main effect of trial ($F_{(5,95)} = 14.78$, $p < 0.00$), a main effect of treatment ($F_{(1,17)} = 6.42$, $p = 0.02$) and a significant interaction between trial and treatment ($F_{(5,95)} = 4.93$, $p < 0.01$). Further analysis using t-test showed that the response latency on the first trial in morphine group was significantly longer than that in saline group ($p < 0.05$), while in the second trial, the latency difference between two groups only approached significance ($p = 0.085$). After two trials, the response latency was significantly reduced in morphine group (trial 1 versus trial 3, trial 4, trial5, trial 6 and trial 2 versus trial 4, trial5, trial 6; $p < 0.01$); and in saline chicks (Trial 1 versus trial 5, trial 6; $p < 0.01$; trial 2 versus trial 5, 6; $p < 0.05$).

The test chick in front of the barrier behaved in a quite stereotyped way: The moment it saw the goal chicks, it moved horizontally along the Plexiglas wall keeping eyes oriented toward the goal, attempting to pass through the barrier; after a while it suddenly turned around, faced the opening of the barrier, and turned either right or left. However when faced with the problem for the first time, the chick exhibited some sort of emotional response to the novel environment: freezing. We recorded the duration of freezing (from the moment it was placed into the apparatus until it showed the typical behavior pattern mentioned above) in both groups, and found that the reaction of saline chicks was significantly faster than morphine exposed chicks (morphine chicks 27.90 ± 8.50 s, saline chicks 6.9 ± 1.13 s, $F_{(1,19)} = 6.61$, $p = 0.02$).

3.1.2. Direction of detour response

Lateral asymmetries in the direction of detour responses are shown in Fig. 3. The ANOVA revealed significant main effects of treatment ($F_{(1,19)} = 5.71$, $p = 0.03$). Saline chicks showed a overall bias to detour the barrier on the left side ($t_{(10)} = -2.80$, $p = 0.02$), while morphine injected chicks seemed to have a bias to detour on the opposite side, however this right side preference did not approached significance. On the first detour trial, choices for left and right directions were evenly distributed (6 chicks went right, 5 left) in saline chicks. On the contrast, 8 out of 10 morphine chicks prefer right ($X_1^2 = 3.60$, $p = 0.058$). Chicks could alternate the directions of detour in a series of six consecutive trials, indicating that they acquired a general strategy rather than a fixed sequence of left–right turning.

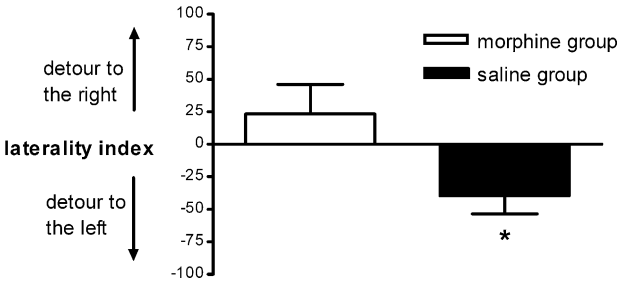

Fig. 3. The direction of detour response. Bars represent the different laterality index of two groups. Group means with S.E.M. are shown. Significant departure from chance level (0) is indicated by the asterisks (*$p < 0.02$; two-tailed one-sample t-tests).

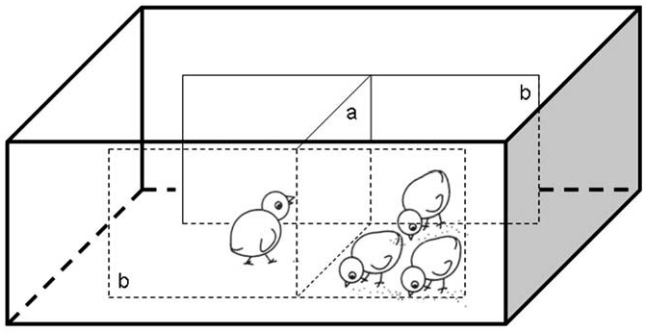

Fig. 4. The schematic diagram of detour learning apparatus used in experiment 2. Note that the apparatus is separated into two compartments by a barrier ("a": transparent Plexiglas wall, "b": opaque wall). To return to the social side, isolated subject has to learn to turn away from the transparent wall and detour through the open tunnel.

3.2. Experiment 2: effect of prenatal morphine exposure on detour learning in chicks

The detour learning results were shown in Fig. 5. Prenatal morphine exposure did not impair acquisition and recall of the spatial memory in repeated detour learning paradigm. The two-way repeated-measures ANOVA analysis showed that there was a

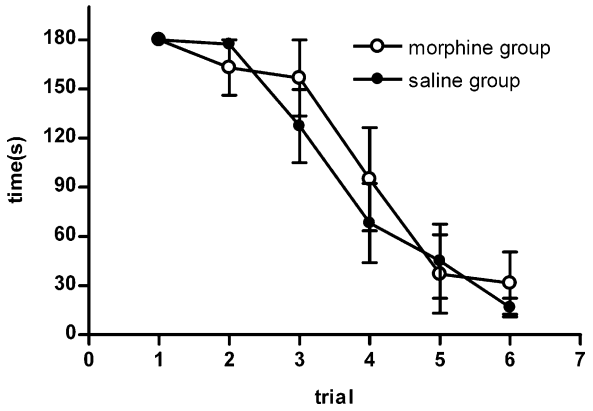

Fig. 5. The effect of prenatal morphine exposure on detour learning. Each point depicts the mean latency for a group of chicks to make a detour around the barrier in experiment 2. There is no difference between morphine exposed ($N = 7$) and saline exposed ($N = 10$) chicks.

main effect of trial ($F_{(5,75)} = 34.94$, $p < 0.00$), but no interaction between trial and treatment, and no main effect of treatment. Similarly, prenatal exposure to morphine had no effect on detour latency for each trial. Both groups could learn and perform the detour learning task perfectly. The latency for finishing the task decreased with the number of trial. In addition, we compared the number of trials required for each chick to detour successfully, still the result indicated no difference between two groups (morphine chicks 3.00 ± 0.45, saline 2.80 ± 0.38, $F_{(1,15)} = 0.11$, $p > 0.05$).

4. Discussion

The present study examined the effects of prenatal morphine exposure on detour behavior in 11-day-old chicks. We found that one-trial detour behavior was affected in prenatal morphine exposed chicks, reflected by longer latency to detour during the first two trials and an altered side preference (a measure of brain lateralization). Because no difference in detour latency was observed between prenatal saline and morphine exposed animals in experiment 2, it could be concluded that prenatal morphine exposure did not affect the spatial learning and memory ability in the detour learning task.

Our results are in accordance with previous evidence showing that provided with certain perceptual and motivational factors, chicks could successfully master detour problem on the first time they encounter the situation (experiment 1) and stronger motivation would make the detour task more difficult, thus required many trials of reinforced learning to accomplish such a ability (experiment 2) (Regolin et al., 1994).

In experiment 1, although both groups could solve the detour problem on the first trial, the latency of morphine group was much longer for the fist two trials compared with saline group. The explanation would attribute to their impaired cognitive abilities to detect, reason, and choose the correct location and/or simply their distinct emotional state, or even some sort of motor dysfunction (this could not be the case since the detour latencies in morphine and saline chicks were almost the same after 3 trials and no obvious difference was found in detour latency in experiment 2). On the first trial of experiment, chicks had no previous opportunity to explore the environment and morphine exposed chicks exhibited longer freezing time than saline chicks, we therefore suspect that the difference may caused by a stronger emotion response in prenatal morphine exposed chicks to novelty: stress response.

Stress responses are an array of adaptive physiological changes elicited by negative or positive stimuli. One of the key neurochemical mediators of stress responses in the CNS is norepinephrine (NE) (Glavin, 1985). Series of studies by Vathy and co-workers (Rimanoczy and Vathy, 1995; Vathy, 1995; Vathy and Katay, 1992; Vathy et al., 1994) consistently demonstrate that exposure of pregnant rats to morphine during mid to late gestation induces long-term, sex-specific alterations in the opioid and NE systems of the exposed adult progeny. Furthermore, those long-term alternations are localized in several brain regions known to participate in the regulation of stress responses and the maintenance of homeostatic balance between the external environment, the brain and the rest of the body (Vathy, 2002). In relevant to the present study, opiate receptors (μ and δ) in developing chick embryo first present as early as E5 (Geladopoulos et al., 1987); complete HPA portal plexus is established on E12 (Jenkins and Porter, 2004), and further became fully functional several days prior to hatching (Vandenborne et al., 2005). Thus, it is possible that prenatal morphine exposure on E12–E16 may modify the capacity of endogenous stress systems to effectively respond to exogenous stressors, especially the HPA axis response (Lesage et al., 1996; Slamberova et al., 2004) to the environmental stress in detour behavior test.

Saline chicks showed orientation lateralization toward left in experiment 1 while prenatal morphine exposed chicks preferred to turn right. Since the arena was symmetrical, no direction of turn was more successful, the bias may represent brain asymmetry. Brain lateralization refers to a phenomenon that includes handedness and superior cognitive abilities, a special trait shared by many species of vertebrates including fish, chick and human (Vallortigara et al., 1999b). Human individuals addicted to heroin exhibit a clear changed bias for their hands, feet, eyes and ears (Mandal et al., 2000). A similar rightward bias of heroin-dependent patients has also been found in a map-picture-following spatial task (Wang et al., 2007), suggesting different impacts of opioids on two cerebral hemispheres. Domestic chicks in semi-natural conditions actively move out of sight of the mother on day 11 (Vallortigara et al., 1999a), a period corresponded with a shift to right hemisphere dominance (Rogers and Ehrlich, 1983). The right hemisphere is supposed to be predominantly involved in spatial processing of the chick (Rashid and Andrew, 1989), such as encode information on the relative position of objects (Tommasi and Vallortigara, 2001). Since the detour behavior requires spatial representation of the goal, the bias of toward right in morphine exposed chicks may imply a potential right-hemisphere dysfunction by prenatal morphine exposure.

We have studied the effect of morphine administration during the prenatal development on memory consolidation in newly hatched chicks (Che et al., 2005). The same dose of morphine used neither has any effect on the development of chick embryo (as there was no reduction in hatching, body weight and the length of incubation), nor sensorimotor development of the neonate, and yet long-term memory in one-trial passive avoidance task is significantly impaired by the prenatal treatment procedure. The memory impairment effect seems inconsistent with the result reported in the present study. However there are several possible interpretations. For instance, different brain regions are involved in these two memory paradigm, while passive avoidance task causes a molecular cascade in intermediate medial mesopallium (IMM) and medial striatum (MSt) (Reiner et al., 2004; Rose, 2000); in detour learning paradigm, although no specific region has been reported, hippocampus may be the potential candidate for this spatial model of learning and memory. In addition, developing animal shows great repair ability. Neonatal impairment does not mean that the insult may last life-long, rather offset effects have always been seen in pervious reports (Spear et al., 1989).

In conclusion, the present study indicates some similarity of effects in avian species to those seen in the mammals and human, suggesting that this species might be useful as a model for rapid exploration of common mechanisms in behavioral disruption. Since we did not exam gender difference, which was widely considered by researchers (Vathy, 2002), further studies might benefit from accounting for sex. In the end our results, together with other animal and human studies, suggest that prenatal exposure to opioids could lead to subtle and specific changes in postnatal behavior, thus raise attention to the possible health hazard from pregnancy drug use in everyday life.

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