Behavioural Processes 103 (2014) 1–4

Contents lists available at ScienceDirect

Behavioural Processes

journal homepage: www.elsevier.com/locate/behavproc

The dominant/subordinate relationship between mice modifies the approach behavior toward a cage mate experiencing pain

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ARTICLE INFO

Article history:
Received 20 May 2013
Received in revised form 2 October 2013
Accepted 21 October 2013
Available online 30 October 2013

Keywords:
Pain
Social cognition
Social dominance
Social preference

ABSTRACT

Many species display approach behavior to conspecifics. This study evaluated approach behavior exhibited by mice toward a cage mate in pain according to the social relationship between the mice. The relative dominant/subordinate relationship among three cage mates was determined using a competitive food retrieval test. Social preference of the subordinate mouse for the mid-status or dominant cage mate was tested with and without pain induced in the dominant cage mate. Social preference of the dominant mouse was similarly tested with and without pain induced in the subordinate cage mate. Subordinate mice spent more time with the dominant cage mate in pain than with the mid-status cage mate but spent a similar amount of time with dominant and mid-status cage mates that were not in pain. Dominant mice spent a similar amount of time with subordinate and mid-status cage mates regardless of pain. The time that subordinate mice spent with the dominant cage mate in pain inversely correlated with dominancy distance between the two mice. These results demonstrate that social relationship can modify perception of the pain of others.

1. Introduction

Social animals may display differential approach behavior toward conspecifics. In rodents, such social preferences are affected by several factors including developmental stage (Panksepp and Lahvis, 2007), environmental context (Pearson et al., 2010), housing (Douglas et al., 2004), and social status (Van Loo et al., 2001). Rodents display social buffering, whereby the presence of a conspecific mollifies the response to distress (e.g., Kiyokawa et al., 2004). Langford et al. (2010) reported that female mice approached a familiar same-sex conspecific in pain more frequently than they approached an unaffected conspecific. Male mice did not display such behavior. Contact with the free mouse resulted in fewer displays of pain by the affected mouse, but only if the animals were unfamiliar cage mates (Langford et al., 2006). Approach behavior to a cage mate may be a type of rescue behavior, or may indicate that the pain response induced curiosity. The tendency to stay close to a suffering cage mate may also be a manifestation of preconcern, whereby an animal is attracted to another's pain (De Waal, 2006). However, approaching a conspecific that is displaying pain or sickness may be dangerous, owing to the possibility of infection from the sick animal. Acute infection by virus or bacteria induces sickness behaviors, and although female mice were able to discriminate and avoid conspecifics with endotoxin-induced inflammation, this was only after prior priming with 1,5-diaminopentane that signaled the presence of a possible decaying corpse in the environment (Renault et al., 2008).

In fact, distress of a conspecific has an aversive property, and animals make efforts to avoid conspecific in distress (Panksepp and Lahvis, 2011). A pain response of conspecifics suppressed operant behavior that had been maintained by food reward in rats (Church, 1959) and pigeons (Watanabe and Ono, 1986), and in a choice experiment, rats avoided pressing a lever that was associated with playback of conspecific vocalization induced by electric shock (Otsuka et al., 2009). Kiyokawa et al. (2006) reported that rats placed in a box in which their cage mates had received an electric shock showed more freezing than control rats, suggesting emission of the alarm pheromone by the cage mates. Mice preferred odors from a non-stressed conspecific to those from a stressed conspecific (Carr et al., 1980); moreover, distress of a conspecific caused a change in heart rate of mice (Chen et al., 2007), and observation of a conspecific being attacked by biting flies increased corticosterone levels in mice (Kavaliers et al., 2003).

I previously evaluated the social preference that mice demonstrated for a distressed cage mate (Watanabe, 2012). Conditioned place preference, in which one part of the environment was associated with a cage mate in pain, resulted in conditioned aversion, not conditioned preference, to the area associated with the cage mate in pain (Watanabe, 2012). However, detailed examination of individual data revealed that some mice showed conditioned aversion whereas others did not. Schadenfreude in humans occurs when the failure or misfortune of demonstrators induces

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http://dx.doi.org/10.1016/j.beproc.2013.10.005

pleasure in the observer. This term is derived from German word "Schade", which means sorry, and "Freude", which means pleasure. Passive observers of lower status experience Schadenfreude when observing failure of a higher-status achiever (Feather and Nairn, 2005; Feather, 2008), suggesting that the social relationship between observer and demonstrator may be crucial in inducing Schadenfreude in humans. Social status, or dominant/subordinate relationship, plays a crucial role in social preference in mice (Fichett et al., 2006; Van Loo et al., 2001), and therefore the inter-individual differences previously observed (Watanabe, 2012) might be caused by differences in the social relationship between the mice. The aim of this study was to evaluate the social relationship (dominant/subordinate) among mice and examine the approach behavior exhibited by mice toward a cage mate in pain according to this relationship.

2. Materials and methods

2.1. Subjects

Thirty male C57/BL6 mice were used. They were obtained from the Nihon Biomaterial Company and were 8 weeks old at the beginning of the experiment. The mice were housed in a room under reversed 12D/12L lighting conditions with temperature maintained at 24 °C. Food and water were freely available, and cheese was given for 5 days before the behavioral test. Each cage contained a group of three mice, and they lived together for more than 2 weeks before the start of the experiment. All mice were treated in accordance with guidelines of the Japanese Society for Animal Psychology. On the day prior to behavioral testing, food was removed from the cage at 18:00 h to cause mild deprivation.

2.2. Apparatus

The apparatus used for the social dominance test was a rectangular acrylic box (40 × 60 × 20 cm) with three compartments (20 × 20 cm each). The center area had a guillotine door (6 × 6 cm) on the wall to each side compartment. The doors were acrylic plate with many holes (5-mm diameter with 3 mm between holes) and were manually opened.

The apparatus used for the social preference test was a conventional conditioned place preference apparatus (MED ENV3015) with three compartments: two side compartments (16 × 13 × 12 cm) and a center compartment (6 × 13 × 12 cm). The center compartment was connected to the two side compartments by guillotine doors. A grey acrylic plate covered the walls and floor of the two side compartments so that they provided identical environments. In each side compartment, a partition was placed 5 cm from the end wall to create a stimulus area. The partition was made of transparent acrylic with many holes (5-mm diameter with 3 mm between holes. The MED–SKED system was used to control the experiment. White noise (75 dB) was broadcast throughout the experiment.

2.3. Procedure

2.3.1. Social dominance test

Several methods have been used to determine dominant/subordinate relationships in rodents (see Scott, 1966). This study employed a food competition test, which is functionally similar to a tube test (Lijam et al., 1997). A food competition test enables clear definition of the winner and loser. The test consists of a 2-day adaptation phase, followed by dominance testing on day 3. The test was administered to each mouse. The mouse was placed in an acrylic cylinder (5 cm diameter, 10 cm long) that was placed just in front of the door of one of the side compartments. After 2 min the door was opened and the mouse could enter the center area, which contained a small (0.4 g) piece of cheese at the center. The next day, the same procedure was repeated using the other side compartment. For the dominance test, two of the three mice from a cage were placed in separate acrylic cylinders, and the cylinders were placed in opposing side compartments. After 2 min, the doors to the central area were simultaneously opened. The mouse that reached and ate the piece of cheese first was defined as the winner, but if the other mouse recaptured the cheese before it was eaten, it was defined as the winner. Mice underwent several tests in one day. The test was administered five times to each pair of cage mates thus, each mouse received the test 15 times in total. The order and side of the side compartments were randomly assigned. The number of wins was counted for each mouse, and the mice in each group were classified as dominant, mid-status, and subordinate according to the highest, middle, and lowest number of wins.

2.3.2. Social preference tests

Two social preference tests were performed: A social preference test for subordinate mice and a social preference test for dominant mice. Each social preference test was performed with and without a formalin injection to induce pain, as detailed below. The order of the four tests was randomized. The floor and walls of each compartment were wiped with 70% ethanol after each test.

In the social preference test for subordinate mice, the dominant and mid-status mice were used as the stimulus and the subordinate mouse was used as the subject. The dominant mouse was placed in one side compartment, in the area separated by the partition. The mid-status mouse was placed in the other side compartment, in the area separated by the partition. The compartments were randomly assigned. The subordinate mouse was placed in the central compartment. After 5 min the doors to the side compartments were opened and the subordinate mouse was free to move around for 15 min. Staying time at each compartment was measured by photosensors attached to the apparatus. In the formalin experiment the paw of the dominant mouse was injected with formalin just before the mouse was placed in the compartment, but the mid-status mouse did not receive any injection. In the control experiment neither the dominant nor the mid-status mouse received any injection.

In the social preference test for dominant mice, the mid-status and subordinate mice were used as the stimulus and the dominant mouse was used as the subject. The procedure was identical to the social preference test for subordinate mice. In the formalin treatment the paw of the subordinate mouse was injected with formalin just before the mouse was placed in the compartment, but the mid-status mouse did not receive any injection. In the control experiment neither the subordinate nor the mid-status mouse received any injection.

2.4. Pharmacological procedure

The formalin injection was used to cause pain, and the procedure employed was similar to that used by Abbott et al. (1999). Formalin (4%; 0.025 ml) was subcutaneously injected into a hind paw of the mouse through a 27-gauge needle connected to a syringe.

3. Results

There was one case in which two mice in a group had the same score in the social dominance test. This group was excluded from further study; therefore, the social preference tests were performed in nine groups of mice. The average score (number of wins) in the dominance test was 2.81. The average score of the dominant and subordinate mice was 7.9 and 2.4, respectively, and this difference was significant ($t(10) = 11.3$, $P < 0.0001$). Fig. 1 shows the results of