Journal of Neuroscience Methods 228 (2014) 27–34

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

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

Basic Neuroscience

A novel semi-automated apparatus for measurement of aggressive biting behavior in mice

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HIGHLIGHTS

- We developed an ARM (Aggression Response Meter) for evaluations of aggressiveness in mice.
- Aggressive biting behavior (ABB) toward inanimate objects was used as a paradigm.
- ARM can detect aggressiveness in the early stages of psychiatric disorders in mice.
- ARM can be used for the evaluation of ABB in both male and female mice.
- ARM can measure ABB repeatedly using the same individual over a long period of time.

ARTICLE INFO

Article history:
Received 23 May 2013
Received in revised form 25 February 2014
Accepted 26 February 2014

Keywords:
Aggressiveness
Isolation-reared mice
Drug evaluations
Anger responses toward inanimate objects
Effects of psychotropic agents
Female

ABSTRACT

Background: Currently, behavioral research of aggressiveness is often conducted with intraspecific inter-male aggression tests. Intraspecific aggression is not detectable in early stages of psychiatric disorders or in female animals, except during the nursing period.
New method: We developed a semi-automated apparatus (ARM: Aggression Response Meter) for measurement of aggressive biting behavior (ABB) in mice. The apparatus is loaded with computer-controlled sticks that stimulate the mouse through touch, inducing irritation and anger. When the mouse bites the sticks in anger, a load sensor attached to the sticks detects ABB dynamically. Changes in ABB were assessed with isolation-reared/re-socialized mice using the ARM, and additional isolation-reared mice were tested using both the ARM and the resident-intruder test, and then buspirone, a serotonin 1A receptor agonist, was administered.
Results: ABB significantly increased during isolation rearing, and then significantly decreased throughout the re-socialization period; both changes were time-dependent. The ARM also detected ABB of female mice after 3 weeks of isolation rearing. Buspirone significantly inhibited aggressive behavior in both tests in a similar manner.
Comparison with existing method: The ARM detects aggressiveness in psychiatric disorders at an earlier stage and in both male and female mice.
Conclusions: ABB toward inanimate objects is a reliable paradigm that makes it possible to detect aggressiveness in the early stage of psychiatric disorders. The ARM is useful for the quantification of aggressiveness using the same individual repeatedly, and for objective evaluation of the effects of drugs on aggressiveness. The ARM can be used with both male and female mice.

1. Introduction

Aggressiveness is a common symptom in patients with psychiatric disorders and developmental disorders. Behavioral assessment of aggressiveness in laboratory animals is essential for the analysis of aggression mechanisms and evaluation of the action of psychotropic drugs.

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http://dx.doi.org/10.1016/j.jneumeth.2014.02.017
0165-0270/

Currently, behavioral research of aggressiveness is often conducted with intraspecific intermale aggression tests using one set of male laboratory animals, such as a resident-intruder test (Blanchard and Blanchard, 1977; Malkesman et al., 2006; Mineur et al., 2003; Mucignat-Caretta et al., 2004; Vergnes et al., 1986). Generally, in intraspecific intermale aggression tests, an intruder mouse is introduced into a resident home cage and the behavior of the mice is observed. Then, evaluations of aggressiveness are carried out based on behavioral paradigms including biting attacks, wrestling, tail rattles, lateral threats and/or latency until the first attack of the intruder (Ibi et al., 2008; Koike et al., 2009; Sakaue et al., 2001).

Intraspecific aggression tests can be used only for male laboratory animals, since females typically do not display aggression toward strangers unless they have pups (Svare and Gandelman, 1976). It is conceivable that intraspecific aggression is dependent on the dynamic state of the male hormones. Thus, it is necessary to establish a method to measure aggressive behaviors unrelated to sexual hormones, since many psychiatric diseases accompanied by aggressiveness are unrelated to sex.

Certain psychiatric animal models are known to attack inanimate objects that touch their body or that move in front of their eyes (Sofia, 1969; Tsuda et al., 1988; Uchida et al., 2009). Indeed, when an experimenter touches such an aggressive animal with a stick repeatedly in its home cage, the animal often attacks the stick by biting it. This behavior is observed not only in males, but also in females. Because this aggressive biting behavior (ABB) is hardly observed in normal laboratory animals, it is considered that ABB is one sign of a psychiatric disorder. In the present study, we focused on this aggressive behavior. We attempted to use ABB as a behavioral paradigm of aggression.

We developed a semi-automated apparatus for the measurement of ABB to assess aggressiveness in mice without an intruder mouse. The apparatus functions as a mechanical touch stimulator and an aggressive biting response detector. It is loaded with sticks to give light touch stimulations to a mouse, and then to induce irritation and anger. When the mouse bites the sticks in anger, the load sensor attached to the sticks detects ABB dynamically. To evaluate the capacity and reliability of the apparatus, we measured changes in ABB under stress induced by social isolation. We also examined the influence of repeated tests using the same individual animal, and evaluated the effect of an antipsychotic drug on ABB using the apparatus. Moreover, we also measured ABB of female mice following long-term social isolation.

2. Materials and methods

2.1. Apparatus

The semi-automated apparatus for measuring ABB in mice, which we developed, is called the Aggression Response Meter (ARM); a schematic and photograph are shown in Figs. 1 and 2, respectively. The outer frame (23 cm × 27 cm × 16 cm) contains a load sensor (Figs. 1-*1, 2A-*1: Tec Gihan Co. Ltd., Kyoto, Japan), a pair of metal sticks for applying light touch or visual stimulation to a mouse (Figs. 1-*2, 2A-*2), a stick-driving unit for moving the sticks (Figs. 1-*3, 2A-*3), and a drive-sliding unit with a pair of rails (Figs. 1-*4b, 2A-*4b) and a knob (Figs. 1-*4a, 2A-*4a) for shifting the stick-driving unit. A transparent, acrylic, cylindrical animal chamber (Figs. 1-*5, 2A-*5, 2B) is set on the top of the frame. All parts, including the software but excluding the load sensor, were custom-made (Muromachi Kikai Co. Ltd., Tokyo, Japan).

The animal chamber is 95 mm in length and 35, 40 or 45 mm in inner diameter. A pair of slits is present in the floor of the chamber at an interval of 11 mm (15 mm in center-to-center distance; Fig. 2B-*6). Each slit is 4 mm in width and 90 mm in length. A pair of metal sticks is set on the stick-driving unit perpendicular to the floor of the chamber just below the slits at an interval of 12 mm (15 mm in center-to-center distance). Each stick is 50 mm in length and 3 mm in diameter with a dome-shaped head. The stick-driving unit is controlled automatically with a computer and makes the sticks move in an up-and-down motion through the slits, which is associated with the application of a light touch or visual stimulation to the mouse in the chamber. The stick-driving unit is loaded on the drive-sliding unit in order to be shifted by manual operation to the right and left. When the mouse bites the sticks, the dynamic strength of the biting behavior is detected three-dimensionally by the load sensor attached to the bases of the sticks, as well as the duration of the behavior. The detected data

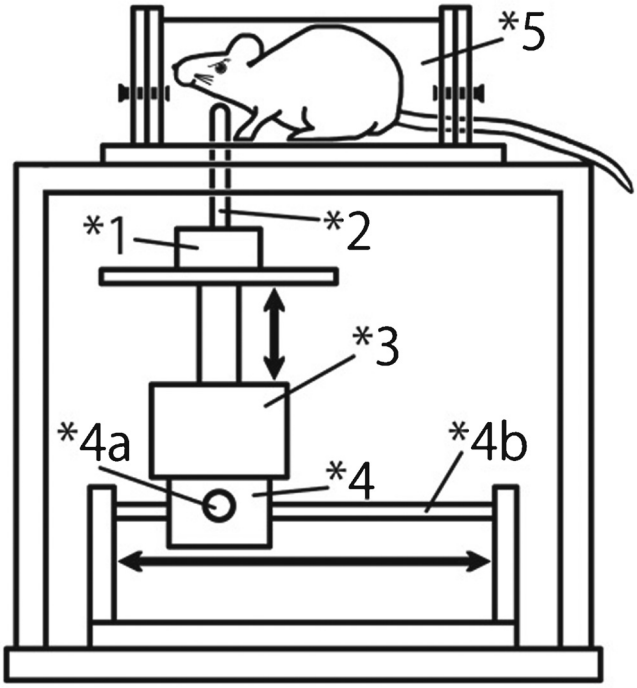

Fig. 1. Schematic illustration of the experimental system (ARM: Aggression Response Meter). The animal chamber (*5) is set on the top of the ARM. The stick-driving unit (*3) is controlled with a computer and makes a pair of sticks (*2) move in an up-and-down motion. The load sensor (*1) attached to the sticks detects the aggressive biting motion of the mouse. The stick-driving unit is shifted on the rails (*4b) of the drive-sliding unit by manual operation to the right and left. (*4) the body of the drive-sliding unit, (*4a) a knob attached to the drive-sliding unit.

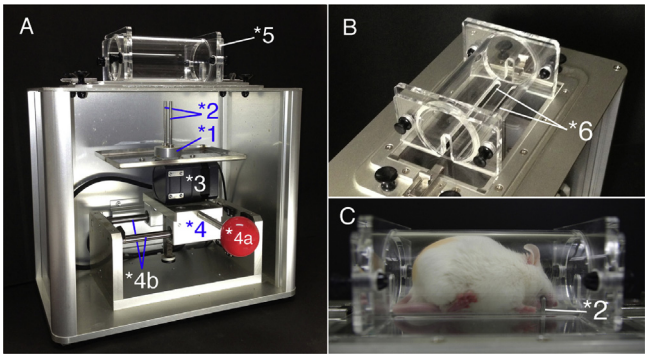

Fig. 2. Photographs of the ARM: (A) general view of the apparatus; *1, load sensor; *2, a pair of metal sticks; *3, stick-driving unit; *4, drive-sliding unit including a knob (*4a) and a pair of rails (*4b); *5, animal chamber. (B) animal chamber placed on the ARM, showing a pair of slits (*6). (C) Photograph showing a mouse exhibiting aggressive biting attack toward a stick (*2).