ELSEVIER

Neurobiology of Aging 33 (2012) 2431–2439

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Age-associated learning and memory deficits in two mouse versions of the stone T-maze

Paul J. Pistell[a,c,*], Edward L. Spangler[b], Bennett Kelly-Bell[b], Marshall G. Miller[b], Rafael de Cabo[b], Donald K. Ingram[a]

[a] *Nutritional Neuroscience and Aging Laboratory, Pennington Biomedical Research Center, Louisiana State University System, 6400 Perkins Road, Baton Rouge, LA 70808, USA*

[b] *Laboratory of Experimental Gerontology, National Institute on Aging, National Institutes of Health, 250 Bayview Boulevard, Baltimore, MD 21224, USA*

[c] *Department of Psychology, Towson University, 8000 York Road, Towson, MD 21252, USA*

Received 16 June 2011; received in revised form 17 November 2011; accepted 1 December 2011

Abstract

We have previously reported that a modified Stone T-maze (STM), using escape from water as motivation, was effective in evaluating learning and memory ability in young C57/BL6 mice. Here we report on the effectiveness and sensitivity of the STM in the assessment of age-related learning and memory deficits in mice using either escape from foot shock or water as the motivational manipulations. C57BL/6Nia mice 7-, 12-, 20- and 24-months old received 15 massed trials in the escape from foot shock motivated STM while C57BL/6Nia mice 5-, 12-, and 25-months old were tested in the escape from water STM. Analysis of errors, the main performance variable, revealed similar results in both versions of the task with younger mice making fewer errors. Notably, mice of all ages in the water-motivated version moved quickly through the maze, while all ages of mice in the shock-motivated version tended to wait for shock to be initiated to move forward. Overall, both versions of the STM appear to be sensitive to age-related changes in learning and memory and provide an alternative to other testing paradigms such as the Morris water maze which are susceptible to performance confounds which can lead to uninterpretable results.

Keywords: Aging; Mice; Learning; Memory; Maze

1. Introduction

Behavioral paradigms that reliably evaluate age-related learning and memory deficits in mice have been difficult to establish. This situation can impede progress to develop therapeutics for the treatment of age-associated neurodegenerative disorders affecting learning and memory. Several behavioral tasks have been the mainstay for this research field, specifically, the Morris water maze (MWM) or versions of the MWM (Ashe, 2001; Chacan et al., 2004; Fisher et al., 2003; Van Dam et al., 2008). However, the MWM was designed initially for assessment of learning and memory in the rat. Assessment of learning and memory in mice using the MWM has proven to be problematic, as it is often unclear if decrements are associated with swimming ability or spatial learning capabilities (Ikeda et al., 2005; Whishaw and Tomie, 1997). Although mice can be trained to perform in MWM paradigms, these paradigms can present possible performance confounds, such as shallow learning curves, refusal to swim or stay on the goal platform, thigmotaxic behavior, and motor confounds resulting from swimming ability, fatigue and thermoregulatory difficulties (Hartman et al., 2001; Iivonen et al., 2003; Rogers et al., 1999). Moreover, when using aged mice, additional potential confounds arise due to the possibility of age-associated declines in visual acuity and motor function (Spencer et al., 1995). Performance deficits in this task then can be falsely inter-

* Corresponding author. Tel.: +1-410 704 3483; fax: +1-410 704 3800.
E-mail address: ppistell@towson.edu (P. Pistell).

0197-4580/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
10.1016/j.neurobiolaging.2011.12.004

preted as impaired learning when comparing young mice to aged mice.

Over the course of many years, our laboratory has used the Stone 14-unit T-maze (STM) as a tool for assessing the neurobiology of age-associated cognitive impairment in rats (Ingram et al., 1994; Ingram et al., 1996; Ingram, 1988). Having been introduced to the literature by Calvin Stone in 1929, this maze paradigm is one of the earliest used to examine rodent learning (Stone, 1929). Charles Goodrick at the National Institute on Aging (NIA) was one of the first to use this paradigm to study age-related memory impairment in rats (Goodrick, 1968). In our hands, the STM has proven valuable for drug discovery and development. Data from the STM was used to obtain patents on novel anticholinesterases for the treatment of Alzheimer's disease and advance them to clinical trials (Greig et al., 2000; Kadir et al., 2008; Klein, 2007). The major advantages of the STM are 2-fold: (1) visual ability requirements are minimized compared to other maze paradigms that heavily involve vision, and (2) motivation to perform can be equilibrated across age groups (Ingram, 1988).

Other classes of drugs have also shown efficacy in enhancing learning performance of old rats in the STM including the nitric oxide donor, molsidomine (Meyer et al., 1998a), while the nootropic drug, codergocrine (Walovitch et al., 1987), and the mitochondrial energy enhancer, acetyl-L-carnitine, were not effective (Barnes et al., 1990). Many other studies have been conducted in young rats to demonstrate that STM learning is impaired by inhibition of signaling in muscarinic cholinergic (Spangler et al., 1986), NMDA glutamatergic (Ingram et al., 1992), D_2 dopaminergic (Umegaki et al., 2001), and nitric oxidergic (Meyer et al., 1998a; Meyer et al., 1998b) systems. Impaired learning in the STM is also observed in rats with lesions to the septohippocampal system (Kametani et al., 1989; Kametani et al., 1993), hippocampus (Duffy et al., 2008), striatum (Pistell et al., 2009), and temporal-parietal, but not to striate cortex (Jucker et al., 1990; Spangler et al., 1994) nor the (Spangler et al., 1990). The lack of effects following the lesions to the striate cortex is again a demonstration that visual processing is not a major performance requirement for this maze. In early versions of the STM, motivation to perform was manipulated by food deprivation (Goodrick, 1968). The rat version that we have used extensively was equipped to deliver scrambled footshock as aversive motivation, and the rat has 10 seconds to move through each of 5 maze segments in order to avoid shock onset (contingency reset after each segment).

Over a number of years, we have attempted to either utilize existing tasks (Brooks et al., 2000), or develop new tasks, capable of reliably assessing age-associated declines in learning and memory in mice. All of these tasks proved to be unreliable as they failed to maintain the proper motivational drive required to keep the mice fully engaged in the task, resulting in inaccurate assessment of learning and memory. However, it was noted that in all these failures, the mice appeared to be driven primarily to escape the apparatus.

Based on our observations that escape appeared to be a primary motivational factor in our previous studies of mice in a number of behavioral tasks, we developed a modified version of the STM for mice. An initial study demonstrated that the mouse STM reliably measures learning and memory in young mice, and that they consistently perform in the task (Pistell and Ingram, 2010). In the studies reported here, we demonstrate the ability of the mouse STM to detect age-associated declines in learning and memory using escape from water and footshock as motivational manipulations in two separate versions of the task. Two independent studies were conducted in mice of various ages in separate laboratories. In one laboratory (Nutritional Neuroscience and Aging Laboratory at the Pennington Biomedical Research Center—PBRC), motivation to maintain task performance was established by requiring the mice to wade, not swim, through water to reach a dark and dry goal box allowing the mice to escape out of the water. In the other laboratory (Laboratory of Experimental Gerontology at the National Institute on Aging—NIA), motivation to keep moving was established by using footshock as the negative reinforcement.

2. Methods

2.1. Animals

For all experiments, virgin male C57BL/6Nia mice were obtained from the aging rodent colonies maintained at Charles River Laboratories (Wilmington, MA) under contract from the NIA. Mice at NIA were 7 (n = 8), 12 (n = 10), 20 (n = 5) and 24 months old (n = 9) at testing, while mice at the PBRC were 5 (n = 9), 12 (n = 12) and 25 months old (n = 12) at testing. At both the PBRC and NIA, mice were housed in vivaria under controlled environmental conditions (PBRC 22 ± 2 °C, 70 ± 10% humidity; NIA 21 ± 2 °C, 70% humidity) with a 12-hours light/dark cycle. Mice at both facilities were group housed (PBRC 4/cage; NIA 5/cage) and had ad libitum access to both standard chow (PBRC: Lab Diets, 5001; NIA: NIH-31) and water. Both facilities had sentinel procedures in place and were determined to be free of specific pathogens at the time of the studies. All procedures were approved by the respective Institutional Animal Care and Use Committees of the PBRC and NIA Intramural Research Program (NIA IRP), and followed the NIH guidelines for the Care and Use of Laboratory Animals.

2.2. Apparatus

Both mazes were constructed by the instrument and fabrication shop maintained by the Intramural Research Program at NIA (Baltimore, MD), the stainless steel grid floor and wiring for the NIA maze were purchased from