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Research report

A comparison of the behavior of C57BL/6 and C57BL/10 mice

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Abstract

Selection of an appropriate animal model is a crucial first step in many research programs. The C57BL/6 (B6) mouse is the most widely used inbred mouse strain in biomedical research; this is particularly so in behavioral studies. However, there are several C57BL substrains, all derived from common ancestors. C57BL/10 (B10) mice are superficially almost identical to B6 mice in appearance and behavior and widely used in inflammation and immunology research, yet rarely in behavioral studies. The present study assessed the comparability of behavioral results from these two strains, to determine whether they could be used interchangeably in future behavioral experiments. The results showed that the behavior of B6 mice clearly differed from that of B10 mice: in tests of cognition, species-typical behaviors, and motor coordination the B6 strain performed better. Consequently, B6 mice will probably remain the preferred choice for behavioral studies. Interpretation of results derived from the B10 strain should take into account its particular behavioral characteristics.

Keywords: C57BL/6; C57BL/10; Mice; Burrow; Spontaneous alternation; Coordination

1. Introduction

The success of any research project is greatly dependent on the use of the best tools or models. The 129 strains of mice, for example, provide excellent stem cells, and are thus extensively used for targeted gene disruption by molecular biologists. However, their behavioral performance is generally inferior to that of C57BL/6 (B6) mice [3]. The latter are widely used in behavioral research, and are the most widely used inbred mouse strain, especially for behavioral work (http://jaxmice.jax.org/strain/000664.html). They have been used in studies of the behavioral effects of inflammatory stimuli such as prion disease (scrapie) and LPS (lipopolysaccharide) [6,34]. However, in non-behavioral studies of inflammation, the closely related C57BL/10 (B10) mouse is more commonly used. But almost all behavioral studies employ B6, rather than B10 mice. Yet, B6 and B10 mice share a common ancestry: both derive from a litter bred in 1921 by Clarence Little, who went on to found the Jackson Laboratories, the world's largest mouse supplier [23]. The two strains diverged prior to 1937. So why do behavioral scientists consistently prefer the B6 strain and non-behavioral inflammatory specialists the B10? Is this because the strains are not interchangeable, and, if so, what are the crucial differences? Both strains breed well (although B10s have fewer litters), their size is similar [31, Table 4.1], and they differ little in price, so these factors cannot explain the preponderance of B6 mice in behavioral studies. Ideally, different experimental questions would be addressed in the same strain to enhance comparability of results. The present study, therefore, sets out to assess the comparability of behavioral results from these two strains, to determine whether future experiments could use either of them interchangeably.

There is currently little literature documenting the B10 behavioral phenotype, and even fewer explicit comparisons between the B10 and B6 strains. B10 mice performed poorly in a water maze relative to NZB and NZB × NZW hybrids [33], but as well as B6 in fear conditioning [29]. Crawley et al. [5] classify B6 and B10 mice as good learners in contextual fear conditioning, and consider their Morris water maze performance similar. They also described a marked difference in reactivity between B6 and B10 mice; the latter show two to three times the startle response to an acoustic or tactile stimulus. Although B6 mice show rather lower pre-pulse inhibition to an acoustic stimulus, the response to a tactile stimulus is similar to B10. In interpreting

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these results it should be noted that all C57BL/6 strains suffer from a progressive age-related hearing loss due to the Cdh23^{ahl} gene [38].

A study of plus-maze behavior showed that B10 mice spent a similar amount of time on the open arms as B6 mice [35], so the strains do not differ on this widely used measure of anxiety. B6 mice, however, do seem more sensitive to reward, showing a somewhat higher preference for 10% sucrose solution [19]. Although B6 and B10 mice are known for their high spontaneous alcohol consumption, it has been shown that in both strains this is largely due to a subset of individuals [20].

The goal of the present research was to investigate whether B6 mice reliably differ from B10 mice on a variety of behavioral measures, analogous to inflammation studies where B10 mice show more pronounced development of osteoarthritis and reactivity to collagenase injections than B6 mice [36]. Are these two strains generally not interchangeable, in spite of being closely related, and could such a difference be quantified? The two strains were therefore compared using a systematic behavioral test battery. This approach has been successfully used in previous studies from this laboratory [3,11–13,17].

Limited work on B10 mice has suggested deficits in hippocampal anatomy and function [39]. They were slower than B6 or CF1 mice to find the hidden platform in a Morris water maze, a reference memory task [27]. (But note that this result differs from that of Crawley et al. [5, Table 1). The hippocampus is essential for reference memory ability, which requires the animal to process extra-maze spatial cues [26]. Therefore, our test battery incorporated many cognitive and species-typical tests that are particularly sensitive to hippocampal dysfunction. Mice with hippocampal lesions are profoundly impaired at learning to locate food on a particular, constant arm of an elevated Y-maze, irrespective of which of the two non-baited arms they start from [11]. We, therefore, assessed the two strains on this spatial reference memory task.

Spatial working memory tasks may place even more demand on the hippocampus, and may therefore be preferentially affected by hippocampal dysfunction. In these tasks, the correct choice on each trial is not constant, but depends upon stimuli specific to that trial. In a spontaneous alternation T-maze task, correct alternation depends only on the arm choice on the immediately preceding sample trial, irrespective of all previous trials. Mice with hippocampal lesions have been shown to perform at chance levels in such tasks [11]. The present study, therefore, included tests of both spatial working and spatial reference memory. These themselves can be further dissociated by their differential susceptibility to genetic manipulation of glutamate receptors [1].

For comparison, a third kind of maze task was included to assess non-spatial reference memory. The Lashley III maze (Fig. 1) [18] superficially appears to be a test of spatial reference memory. Mice with hippocampal lesions can, however, solve it [11]. Moreover, the performance of control and lesioned mice was shown to be unaffected when the maze was rotated by 180 degrees relative to the distal visual cues external to the maze. Both findings suggest mice solve this maze using a non-spatial egocentric rule-based strategy ('turn left, right, left, right'), which does not require the hippocampus.

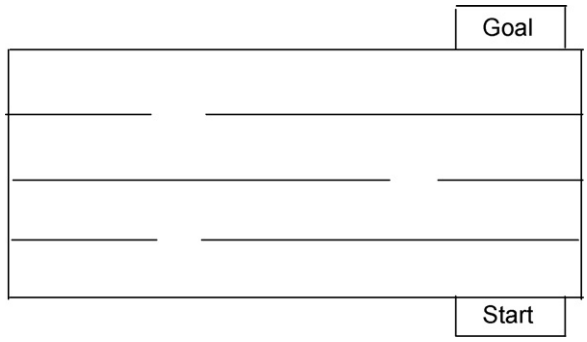

Fig. 1. The Lashley III maze.

Stereotyped behavior has also been noted in rats with hippocampal lesions [15] and has occasionally been seen in this laboratory in hippocampal lesioned mice. Stereotypy is an index of behavioral dysfunction [16]. Therefore, a formal assessment of stereotyped home cage behaviors in B6 and B10 mice was performed.

A range of motor- and species-typical behavior tests were also carried out to ensure that deficits that might be observed in the cognitive tests were not due to non-specific sensorimotor factors. Moreover, we also included a number of species-typical tests that are known to be sensitive to hippocampal dysfunction [13].

There are at least six substrains of B10 mice (C57BL/10ScNJ, /10ScSn, /10Sn, /10Sx, /10WtRk, /10Cr) and five of B6 mice (C57BL/6J, /6By, /6ByJ, /6JEiJ, /6NJ) and numerous commercial suppliers have their own strain, originating directly or indirectly from the Jackson Laboratories. Virtually no behavioral comparisons of substrains appear to have been performed. In the UK, the only available B10 substrain is the C57BL/10ScSn, whereas two B6 substrains are available, C57BL/6J and C57BL/6NJ.

Genetic studies have revealed a number of differences between B6 and B10 strains. They vary at multiple microsatellites over short segments (10 Mb or less) on chromosome 4 [22], and on chromosomes 11 and 13 [32], while a recent study using SNPs has revealed additional variation on chromosomes 2, 3, 8, 14, 15, and 18, again over short segments of DNA (http://www.well.ox.ac.uk/mouse/INBREDS).

2. Method

2.1. Subjects

Ten C57BL/6JOlaHsd and 15 C57BL/10ScSnOlaHsd female mice, 8 weeks old on arrival from the suppliers (Harlan, UK) were housed in groups of five in plastic cages with aspen chip bedding. (Ola and Hsd are abbreviations indicating the past (OLAC) and present (Harlan Sprague–Dawley) commercial breeders of these mice). A cardboard shelter, tunnel, and nesting material (Nestlets) (Lillico, Betchworth, UK) were provided as environmental enrichment. It is now widely accepted that enrichment improves animal welfare and helps normalise behavior, without risk of increased variability of results [40]. Draft Appendix A of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (ETS No. 123, Strasbourg 2004) recommends that social animals should be housed in groups whenever possi-