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Research report

Understanding the behavioural phenotype of the precocial spiny mouse

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HIGHLIGHTS

- The effects of sex and age on the behaviour of spiny mice (*Acomys cahirinus*) were examined in this study.
- Spiny mice were behaviourally characterised on a set of behavioural test commonly used to assess rodent models of disease.
- Spiny mouse demonstrate precocial development of exploratory activity, locomotor coordination and social behaviours.
- Fear and anxiety behaviours, learning and memory, and sensory gating can be assessed from relatively early postnatal development in the spiny mouse.

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ABSTRACT

The use of the spiny mouse (*Acomys cahirinus*) in experimental research is steadily increasing, due to the precocial nature of this species and the similarities in endocrinology to the human. The characterisation of normal behavioural traits throughout development has not been comprehensively measured in the spiny mouse. Therefore the aim of this study was to behaviourally phenotype the spiny mouse, with the use of behavioural paradigms commonly used to assess behaviour in rat and mouse models of human behavioural disorders such as autism, attention-deficit disorder, and schizophrenia. Male and female spiny mice were assessed at 1–5, 10–15, 20–25, 40–45 and 80–85 days of age using the open field test, novel object recognition test, rotarod, elevated plus maze, a social interaction test, and prepulse inhibition. Exploratory activity, motor coordination, fear, anxiety and social behaviours could be accurately measured from 1 day of age. Open field exploration and motor coordination on a modified rotarod were precociously developed by 10–15 and 20–25 days of age, respectively, when they were equivalent to the performance of conventional adult mice. Learning and memory (assessed by the novel object recognition test), and sensory gating (prepulse inhibition) could be reliably determined only after 20–25 days of age, and performance on these tests differed significantly between male and female spiny mice, particularly in adulthood. This study characterises the behavioural traits of spiny mice and provides important information about critical periods of behavioural development throughout postnatal life.

1. Introduction

The use of animal models to study human disease is essential for the better understanding of the disease process, and to develop and test potential treatments. Rats and mice are often used for this type of research, but from a developmental point of view these conventional laboratory rodents do not possess many of the fundamental features of human pregnancy. Many aspects of the newborn human reflect a precocial mode of development; such as relatively complete neurogenesis [1,2] (and organogenesis, in general) by birth, as well as an altricial mode of development in that the infant is highly dependent on the mother for nutrition and mobility for an extended period after birth. This pattern of development is unique to the human. The spiny mouse (*Acomys cahirinus*) is a small rodent-like animal which replicates many of the hormonal characteristics of human pregnancy [3] as well as the precocial mode of organ development, including

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the brain, where considerable neurological maturity is reached at birth [1].

The spiny mouse is a desert rodent species native to regions of Africa and the Middle East. The neonates are precocial, in that they are capable of movement from birth, and self-feeding within 4–6 days after birth [4]. Compared to other rodents, spiny mice are born with a well-developed coat, eyes and ears are open and visual and auditory functions are well developed, together with other sensory [4] and autonomic functions, including thermoregulation [5]. They are capable of locomotion and have vestibular function (i.e., negative geotaxis) from soon after birth (hours), and it is therefore possible to make meaningful quantitative and qualitative assessments of behaviour from postnatal day 1 in this species.

Spiny mice have a relatively long gestation of 38–39 days and a small litter size (usually 1–3) [6]. In addition to the longer exposure to the maternal/intrauterine environment, foetal development is somewhat more comparable to the human in that, unlike rats and mice, the foetal adrenal gland secretes cortisol and dehydroepiandrosterone (DHEA) [3], and DHEA is also synthesised in the foetal and neonatal brain [3]. The presence of cortisol and not corticosterone in this species is indeed a highly significant finding, with various implications for the field of developmental endocrinology, brain–adrenal–placental interactions, and the effects of stress on the developing brain during pregnancy. The fact that the adrenal gland of this animal produces not only cortisol but also small amounts of the androgen DHEA during gestation makes it a better model of human foetal development compared to both conventional rat and mouse species. In addition, the maximum rate of brain growth occurs in the spiny mouse, as in the human infant, at near the time of birth. Neuroanatomically, cortical and limbic development at 30 days (0.75) gestation in the spiny mouse is equivalent to 24–26 weeks gestation in the human infant [1].

The advanced development of the spiny mouse at birth provides an opportunity to assess the contribution of normal and abnormal in utero development on the brain and behaviour postnatally. This is particularly relevant to the growing consensus that neuropsychiatric disorders such as autism and schizophrenia have origins in foetal life [7–9]. However, to fully understand aberrant behaviour in the spiny mouse, it is first necessary to fully characterise normal behavioural traits, and particularly for developmental studies, to describe the changes that occur from the early neonatal period into early adult life. Therefore, the aim of this study was to characterise the development of behaviour from birth in the spiny mouse, with a focus on behavioural paradigms commonly used to identify abnormal behaviour and cognition that, in conventional mice and rats, have been used as models of neuropsychiatric disease.

2. Methods

2.1. Animals

Spiny mice (*A. cahirinus*) were obtained from the breeding colony maintained at Monash University. The mice were housed under controlled temperature ($25 \pm 0.5\,^{\circ}C$) and humidity ($30 \pm 5\%$) conditions, and a 12 h light–dark cycle (lights on at 0700 h), using the breeding protocols previously described [10]. All procedures received prior approval from the Monash University Animal Ethics Committee and were conducted in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

2.2. Behavioural testing procedures

One male and one female spiny mouse were selected from the litters of at least 16 dams and randomly assigned to one of two cohorts for behavioural testings (see Fig. 1A). Cohort 1 pups ($n = 8$ male, $n = 8$ female) were assessed using, in sequence, the open field test, novel object recognition test, rotarod, and elevated plus maze at 1–5 10–15, 20–25, 40–45 and 80–85 days of age. Cohort 2 pups ($n = 8$ male, $n = 8$ female) were assessed using the social interaction test and prepulse inhibition (PPI) at similar ages, except the PPI test was not conducted at the 1–5 days of age. The pups were separated into two cohorts to allow for a 1- to 2-day rest period between tests in each age range to minimise stress effects on behaviour that would have occurred if each animal was to be subjected to all tests [11]. Testing was always conducted between 1000 and 1300 h to avoid diurnal effects [12], and all animals were habituated to the test room and apparatus for at least 30 min prior to obtaining any measurements.

2.3. Open field

The open field test was conducted on the first day of each age range days 1, 10, 20, 30, 40 and 80; Fig. 1). Individual animals were placed in the centre of a square field 50 cm × 50 cm, with 40 cm high walls which are uniformly black and provide no visual cues. Lighting levels were 2.8 lux for all trials. Activity was recorded using a video camera over the next 5 min. Post-acquisition analysis of the activity using CleverSys software (CleverSys Inc., USA) was used to track the movement of the animals throughout the open field trial by identifying the nose, body and tail. This software also allowed the measurement of distance (cm) travelled and time (seconds) spent in the central zone (defined as the area of the field excluding the 10 cm outer perimeter) vs. the outer zone.

2.4. Novel object recognition test

The novel object recognition test (NORT), which assesses non-spatial memory [13], was conducted immediately after the completion of the 5 min open field test which acts as a habituation trial to reduce the contribution of anxiety and stress on the outcome. Two bottles of identical shape, colour and size were placed in the open field approximately 6 cm from the walls of the enclosure to ensure the animal had an unobstructed view of the objects at all times. The animal's behaviour and investigation of the objects was recorded for 10 mins (learning trial), after which the animal was returned to its home cage for a 1 h retention period. During this time one of the bottles was replaced with an object of a different shape and colour (the novel object); both the novel and familiar object were wiped down with 70% ethanol at this time to remove olfactory cues. The animal was then replaced in the open field ('recall trial') and it's behaviour and exploration of the two objects was recorded for the next 10 min. In both the learning and recall trials behaviour was scored as positive, actual investigation when the animal's nose was pointed at, and within 2 cm of the object, as used elsewhere [13–20]. Post-acquisition analysis with the CleverSys software was used to measure the time animals spent investigating the object. The total time spent exploring each object in the recall trial was used to calculate the 'discrimination index', calculated by subtracting the time spent exploring the familiar object from the time spent exploring the novel object, divided by the total time spent exploring both objects. Thus, a discrimination index of 1 indicates that the animal spent all of the time exploring the novel object, 0 indicates no preference for either object, and −1 indicates the animal spent all the time exploring the familiar object.

2.5. Rotarod

A rotarod trial was conducted 1–2 days after the open field and NORT test. A standard rat accelerating rotarod apparatus has an inner axle with a diameter of 2.5 cm with 12 cm walls. This