Behavioural Brain Research 313 (2016) 282–292

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

The impact of maternal neglect on genetic hyperactivity

Petra Majdak[a,b,*], Elizabeth L. Grogan[b], Joseph V. Gogola[b], Anastassia Sorokina[b], Stephen Tse[b], Justin S. Rhodes[a,b,c]

[a] The Neuroscience Program, University of Illinois, 405 North Mathews Avenue, Urbana, IL 61801, USA
[b] The Beckman Institute for Advanced Science and Technology, University of Illinois, 405 North Mathews Avenue, Urbana, IL 61801, USA
[c] Department of Psychology, University of Illinois, 603 E. Daniel Street, Champaign, IL 61820, USA

HIGHLIGHTS

- Selective breeding for hyperactivity severely impairs maternal competence.
- Severely adverse rearing conditions do not influence genetic hyperactivity.
- Severely adverse rearing conditions significantly depress Control activity.
- Severely adverse rearing conditions reduce body mass in hyperactive mice.

ARTICLE INFO

Article history:
Received 2 June 2016
Received in revised form 14 July 2016
Accepted 18 July 2016
Available online 19 July 2016

Keywords:
Selective breeding
Maternal care
Pup retrieval
Postnatal stress
Genetic hyperactivity

ABSTRACT

Early environmental conditions are increasingly appreciated as critical in shaping behavior and cognition. Evidence suggests that stressful rearing environments can have an enduring impact on behaviors in adulthood, but few studies have explored the possibility that rearing environment could exacerbate genetic hyperactivity disorders. Uncovering a strong environmental influence on the transmission of hyperactivity could provide novel avenues for translational research. Recently we developed a selectively bred High-Active line of mice to model ADHD, providing a unique resource to address the question of environmental transmission. The High-Active line demonstrates transgenerational hyperactivity, but the influence of the postnatal environment (i.e. maternal care provided by dams) on hyperactivity had not been systemically quantified. This study employed a cross-fostering method to simultaneously address 1) whether High-Active and Control pups are provided with similar levels of care in the early environment, and 2) whether any differences in rearing environment influence hyperactive behavior. High-Active dams demonstrated impairment in all measures of maternal competence relative to Controls, which reduced survival rates and significantly reduced the body mass of offspring in early life and at weaning. While the deteriorated postnatal environment provided by High-Active dams was ultimately sufficient to depress Control activity, the hyperactivity of High-Active offspring remained unaffected by fostering condition. These data not only confirm the power of genetics to influence hyperactivity across generations, but also provide evidence that early rearing environments may not have a significant impact on the extreme end of hyperactive phenotypes.

1. Introduction

The power of environment to influence complex behavioral phenotypes has generated great interest over the past several decades [1]. In addition to the established influence of genetics (e.g. mutations altering protein expression/function) on phenotype, maternal environment (e.g. histone modification, DNA methylation) may also disrupt the trajectory of normal behavioral and psychological development in individuals predisposed to disease states. Multiple studies have demonstrated significant associations between adversive postnatal environments and the manifestation of clinical disorders later in life [2–4]. Modeling the effects of early life stressors in animals has largely corroborated such results; exposure to maternal separation or neglect heightens stress reactivity, aggression, and other features of clinical disorders such as depression and schizophrenia [5–8]. Accumulating evidence not only suggests that early life environment affects relevant genes via epigenetic modifi-

* Corresponding author at: Beckman Institute, 405 North Mathews Avenue, Urbana, IL 61801, USA.
E-mail address: pmajda2@illinois.edu (P. Majdak).

http://dx.doi.org/10.1016/j.bbr.2016.07.033
0166-4328/

cations which may serve as biomarkers for susceptible populations [9,10], but furthermore that environmentally-induced behavioral deficits may be transmitted to subsequent generations [11–13]. Determining the relative contribution of genes versus environment to the manifestation of a specific behavior is of critical importance for not only elucidating its etiology, but also guiding ongoing endeavors to identify relevant trait-specific biomarkers.

Over the past decade, our lab has maintained a line of mice selectively bred for an extreme hyperactivity phenotype which has shown promise as a model of Attention-deficit/Hyperactivity disorder (ADHD) in recent generations [14,15]. ADHD demonstrates exceptionally high heritability estimates in the range of 70–90% [16,17], therefore we propagated a highly genetically variable line of mice for hyperactive behavior across multiple generations. Additional studies have further validated the High-Active model by demonstrating that their hyperactivity is paradoxically ameliorated by low-dose amphetamine, a psychostimulant commonly used to treat ADHD [14]. However, an important remaining question is whether our assumption, that High-Active hyperactivity is driven purely through genetic factors, is correct. It is possible that some of the hyperactive phenotype is transmitted to offspring through extremely hyperactive dams creating a chaotic, stressful early rearing environment [18,19]. This alternative explanation for the propagation of hyperactivity has never been systemically explored in our line, despite circumstantial evidence for its possibility; across multiple generations, the High-Active line shows impaired reproductive success [14] which has anecdotally been ascribed to High-Active dams providing poor maternal care by engaging in trampling and/or cannibalization behavior. Thus, in order to understand the transmission of hyperactivity in the High-Active line it is critical to 1) assess the quality of High-Active versus Control rearing environments, and 2) determine whether these environments influence the hyperactive phenotype. Evidence of a substantial environmental influence on hyperactivity would support studies suggesting adversive environments exacerbate ADHD-like behaviors [19,20], while a predominantly genetic component to hyperactivity, minimally influenced by environment, would more closely support the construct validity of the High-Active line to model a disorder as highly influenced by genetics as ADHD [16].

In order to parse out the contributions of environment and genetics on home cage activity levels, we employed a cross-foster design to simultaneously address both aforementioned questions. Dams underwent maternal care observations and performed pup retrieval tasks with their assigned litters, which were comprised of a mixture of pups from both lines. This approach allowed us to operationalize the definition of poor maternal care. Evaluating maternal competency and its effect on hyperactivity are of critical importance, not only in understanding the transmission of hyperactivity in our model, but also in providing direct tangible evidence for or against the idea that postnatal environment affects hyperactivity in adulthood. Either outcome, that rearing environment does or does not influence hyperactivity, advances our understanding of the relative influence of genetic versus environmental factors that contribute to variation in physical activity.

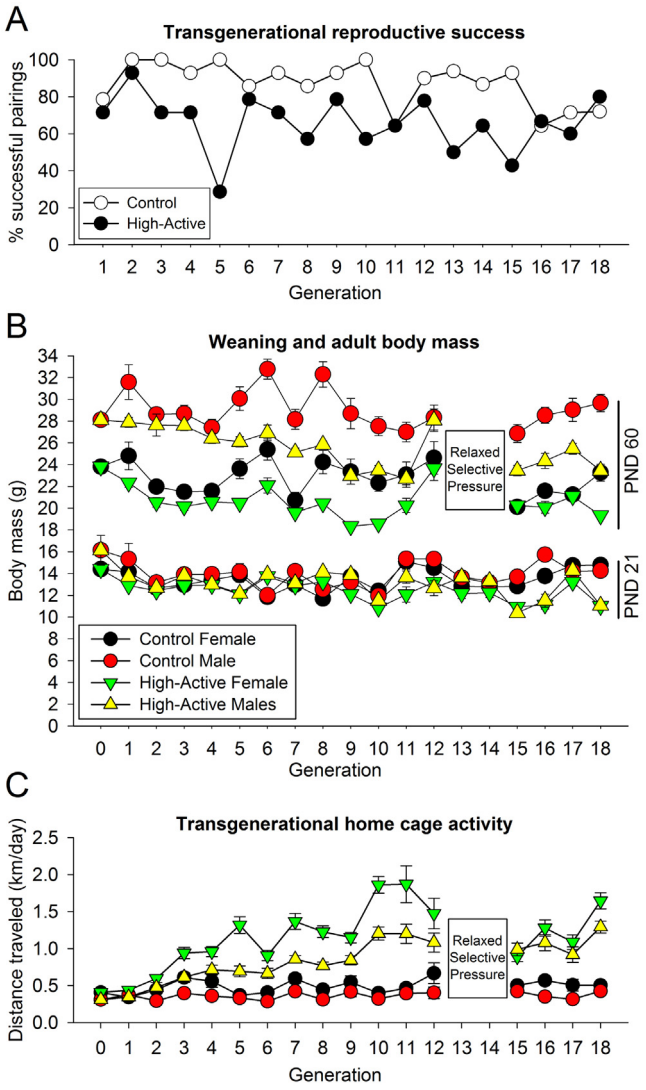

Fig. 1. Transgenerational data.
A. Each data point reflects the percentage of paired mice each generation which successfully contributed offspring to propagate the lines. Typically 14 High-Active and 14 Control pairs were made during each breeding cycle. B. Average body mass in grams (±SEM) at PNDs 21 (weaning) and 60 (adulthood phenotyping) are represented for each generation. During Generations 13 and 14, mice were not phenotyped, therefore adulthood body mass was not recorded (as indicated by the boxed "relaxed selective pressure"). C. Data reflect the average locomotor activity in the home cage in km/day (±SEM) of adult High-Active and Control mice. Each data point reflects the phenotype of between 100 and 200 High-Active and Control mice per generation. Mice underwent distance tracking in the home cage for six consecutive days; the 24-h activity levels on days 5 and 6 of a six-day test were averaged to assess phenotype.

2. Materials and methods

2.1. Animals

2.1.1. Selective breeding and general husbandry

Our lab maintains two lines of outbred mice; a randomly bred, unselected Control line and a High-Active line selectively bred for increased distance traveled in the home cage [14,15]. The starting population for each line was generated from the highly genetically variable Collaborative Cross mice [21]. At approximately postnatal day (PND) 60, mice of each line were phenotyped individually for home cage activity. Custom-made acrylic home cages (18.5 × 33.5 × 16 cm) with clear plastic lids allow for continuous video tracking by TopScan software (CleverSystems, Reston, VA, USA). Each cage individually housed 4 mice, with a wire mesh interaction zone that allowed for limited physical contact. This video coverage allowed for simultaneous tracking of a maximum of 64 individual mice over a 6-day test. After an extended habituation period of 4 days, the average distance traveled during days 5 and 6 was used as the selection criterion for the High-Active line. Controls were randomly bred with respect to distance traveled in the home cage. Selective pressure was not applied to the High-Active line in Generations 13 and 14 (Fig. 1C) due to a lack of resources and per-