



## Early life stress dampens stress responsiveness in adolescence: Evaluation of neuroendocrine reactivity and coping behavior



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### ABSTRACT

Stressful experiences during early life (ELS) can affect brain development, thereby exerting a profound and long-lasting influence on mental development and psychological health. The stress inoculation hypothesis presupposes that individuals who have early experienced an attenuated form of stressors may gain immunity to its more virulent forms later in life. Increasing evidence demonstrates that ELS may promote the development of subsequent stress resistance, but the mechanisms underlying such adaptive changes are not fully understood. The present study evaluated the impact of fragmented dam-pup interactions by limiting the bedding and nesting material in the cage during postnatal days 2–9, a naturalistic animal model of chronic ELS, on the physiological and behavioral responses to different stressors in adolescent mice and characterized the possible underlying mechanisms. We found that ELS mice showed less social interaction deficits after chronic social defeat stress and acute restraint-tailshock stress-induced impaired long-term potentiation (LTP) and enhanced long-term depression (LTD) in hippocampal CA1 region compared with control mice. The effects of ELS on LTP and LTD were rescued by adrenalectomy. While ELS did not cause alterations in basal emotional behaviors, it significantly enhanced stress coping behaviors in both the tail suspension and the forced swimming tests. ELS mice exhibited a significant decrease in corticosterone response and trafficking of glucocorticoid receptors to the nucleus in response to acute restraint stress. Altogether, our data support the hypothesis that stress inoculation training, via early exposure to manageable stress, may enhance resistance to other unrelated extreme stressors in adolescence.

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### 1. Introduction

Stressful experiences during early life (ELS) can affect brain development, which could lead to a profound and long-lasting influence on cognitive and emotional functions, as well as on the susceptibility to developing psychopathology (Loman and Gunnar, 2010; Lucassen et al., 2013; Singh-Taylor et al., 2015). To date, most mechanistic studies have focused on determining the detrimental consequences of ELS on the development of stress-related disorders later in life (Brunson et al., 2005; Murgatroyd et al., 2009; Ivy et al., 2010), but relatively little is known about the adaptive changes in response to ELS that promote the development of stress

resistance and successful psychological functioning (Lucassen et al., 2013). The idea that ELS may induce the development of subsequent stress resistance is consistent with the “stress inoculation hypothesis”, which posits that prior mildly stressful experiences can foster resilience to future stress or trauma (Eysenck, 1983). Retrospective human studies have reported that experienced survivors of floods or earthquakes exhibit lower anxiety and less depressed affect encounters with the same disasters than inexperienced counterparts (Norris and Murrell, 1988; Knight et al., 2000). This hypothesis is also supported by prospective longitudinal studies in nonhuman primates demonstrating that monkeys exposed to brief periods of maternal separation stress exhibited less anxiety-related behaviors and attenuated hypothalamic-pituitary-adrenal (HPA)-axis responses to subsequent stressors compared with unmanipulated control monkeys (Parker et al., 2004, 2006; Lyons et al., 2010). Likewise, neonatal rats exposed to brief maternal separations (3 min per day during the first three weeks of life) exhibited diminished emotionality and attenuated HPA-axis

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responses to stressors in adults (Levine, 1957, 2005). Other rodent studies, however, suggest a role for maternal care in the development of stress resistance, rather than stress exposure per se (Macrì and Würbel, 2006; Meaney, 2010). Indeed, diminished neuroendocrine stress responses were observed in unhandled offspring that naturally received higher levels of maternal care during developmental stages (Liu et al., 1997; Francis et al., 1999). In contrast, some studies have failed to observe a link between the adult offspring regulations and the levels of maternal care (Tang and Reeb, 2004; Tang et al., 2006, 2008). More recently, a novel mouse model for the study of stress inoculation hypothesis has been established using a modified chronic social defeat stress (CSDS) protocol (a 15-min session every other day for 21 days) (Brockhurst et al., 2015). This model has been consistently shown to stimulate corticosterone

response and thereby enhance active stress coping behaviors; however, the mechanisms underlying such adaptive changes have not been resolved.

Previous studies showed that dam-pup interactions in mice could be disrupted by limiting nesting and bedding material in the cage in a dose-dependent manner (Rice et al., 2008; Baram et al., 2012). Fragmentation of dam-pup interactions during the first postnatal week is sufficient to produce enduring neuroendocrine and behavioral changes (Rice et al., 2008). Because the overall duration or quantity of dam-pup interactions is not altered by limiting nesting and bedding material (Rice et al., 2008), this naturalistic mouse model of ELS would provide an advantage of examining the stress inoculation hypothesis without considering the impact of increased maternal care following brief intermittent separations. Furthermore, insofar as very little is known regarding the impact of ELS on the development of stress resistance in adolescence, we therefore used this fragmented maternal care model to investigate the influence of ELS on the physiological and behavioral responses to different stressors in the adolescent offspring and characterized the possible underlying mechanisms. Our results reveal that ELS alters HPA axis reactivity leading to diminished stress responsiveness and enhanced stress coping behavior in adolescence.

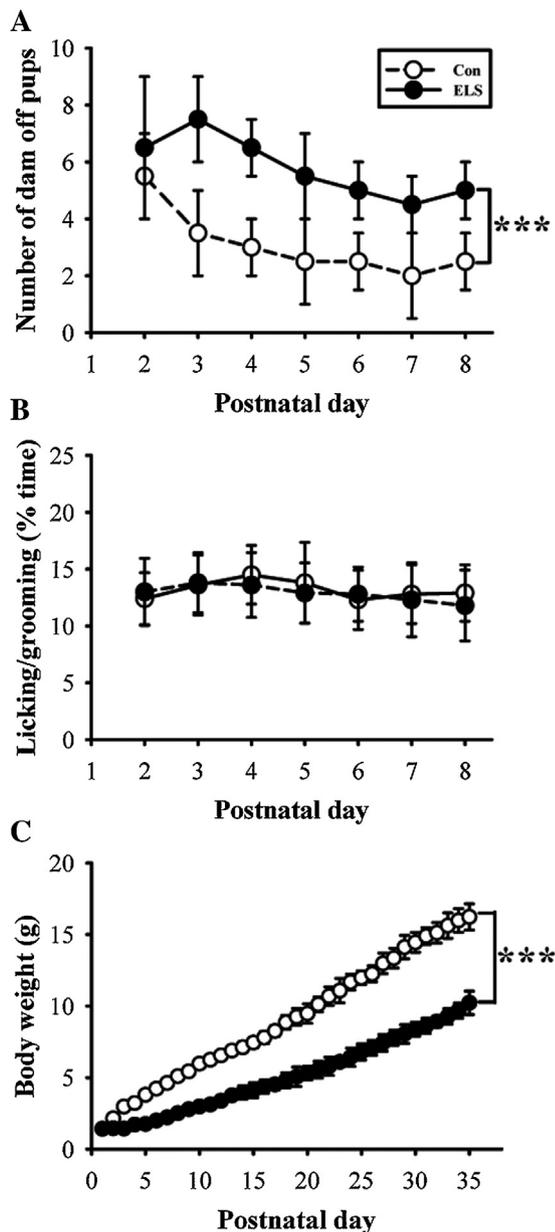
## 2. Material and methods

### 2.1. Animals

Pregnant C57BL/6 mice ( $n=80$  for control group and  $n=82$  for ELS group) were housed individually under controlled illumination (12-h light/dark cycle with lights off at 18:00 h) and ambient temperature ( $24 \pm 2^\circ\text{C}$ , 40% humidity), and had *ad libitum* access to food and water. Pups were born on gestation days 19–21 and the day of birth was termed postnatal day (P) 0. On P1, pups were removed from the nests and five healthy pups that included both genders (three males and two females) were randomly placed back with each dam. All behavioral tests were performed during the light cycle between 9:00 h and 15:00 h. At the day of testing, experimental mice were transferred to the experiment room and allowed to acclimate for approximately 3 h before testing. To avoid variability caused by hormonal cycles in females, only male offspring were used in this study. To avoid litter effects, only one offspring per dam was used in each experiment. In addition, all mice were used only once for an individual behavioral task. If any pup died during the lactation period, all other offspring were sacrificed immediately and were not included in the study. All experimental procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of National Cheng Kung University.

### 2.2. Adrenalectomy and corticosterone replacement

Adrenalectomy (ADX) was performed via small bilateral dorsal flank incisions under isoflurane anesthesia as previously described (Chen et al., 2010). ADX mice received replacement corticosterone ( $10 \mu\text{g/ml}$ ) in drinking water containing 0.9% saline immediately after surgery. Corticosterone was first dissolved in 100% ethanol and then diluted 1000 times in drinking water containing 0.9% saline. Mice were used for experiments 1 week after surgery. Control mice underwent a sham surgery with the same surgical procedure as the ADX mice, except that the adrenal glands were not removed. Successful ADX was verified by measurement of plasma corticosterone levels. Only mice with plasma corticosterone concentrations  $< 1 \mu\text{g/dL}$  were considered successful and included in data analysis.



**Fig. 1.** Reduced bedding and nesting material in the cage influences the interactions mouse dams with their pups. (A) Summary graph showing the average number of dam off pups from control (Con) and ELS dams through P2–P8. (B) Summary graph showing the percentage of time spent in maternal licking/grooming behaviour from Con and ELS dams through P2–P8. (C) Summary graph showing the body weight of Con and ELS mice during P1–P35. Data are represented as mean  $\pm$  SEM. \*\*\* $p < 0.001$  compared with Con group.

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