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Strain vulnerability and resiliency in the chick anxiety–depression model

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HIGHLIGHTS

- Strain differences were assessed in the chick anxiety–depression model.
- Social isolation produced differences in onset of depression thresholds.
- Black Australorp strain was determined to be a vulnerable genetic line.
- Production Red strain was determined to be a resilient genetic line.
- Intermediate responsivity was the Silver Laced Wyandotte strain.

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ABSTRACT

Increasing research is focused on genetic contributions to variability in stress-related endophenotypes in humans and animal model simulations. The current study sought to identify strain vulnerabilities and resiliencies to an isolation-stressor in the chick anxiety–depression model. Nine different strains of socially raised chicks were tested in isolated or non-isolated conditions for 90 min in which distress vocalization (DVoc) rates were collected and then transformed to depression-like phase threshold (@ 25, 50, 75 and 95%) latencies. In general, chicks in the non-isolated condition displayed relatively low DVoc rates throughout the test session, despite some variability in initial rates. Chicks in the isolated condition displayed relatively high DVoc rates in the first 3 min, indicative of an anxiety-like state, which declined by approximately 50% within 10–25 min in all strains and remained stable thereafter, indicative of a depression-like state. Contrast effects revealed that, relative to all other strains, the Black Australorp strain displayed shorter and the Producrain displayed longer depression threshold latencies, respectively. Of the remaining strains, the Silver Laced Wyandotte displayed depression thresholds that best represent an intermediate stress response. These findings identify vulnerable and resilient strains for examining depression-related endophenotypes in the chick anxiety–depression model.

1. Introduction

Anxiety and depression are common and debilitating clinical disorders. While many patients show clinical improvement with anxiolytics and antidepressants, these drugs may produce unpleasant side effects, and a significant number of patients are unaffected by current pharmacotherapeutic options [1–4]. Understanding the neurochemical underpinnings and treatment targets relies, in part, on valid animal model simulations. Common rodent models of anxiety and depression include the elevated plus maze and the forced swim test, respectively. However, these paradigms fail to model the current understanding that anxiety and depression are related clinical syndromes [5–7].

The chick anxiety–depression model [8] is a hybrid simulation of both syndromes in a single paradigm. The procedure involves an isolation stressor that initially produces high distress vocalization (DVoc) rates characteristic of an anxiety-like state [9–11]. This is followed by lower DVoc rates, characteristic of a depression-like state (i.e., behavioral despair) [12]. This model possesses face, construct and predictive validity in that these phases are pharmacologically dissociated in that diverse compounds possessing anxiolytic effects (e.g., chlordiazepoxide, clonidine and imipramine) attenuate the high DVoc rates during the anxiety-like phase while compounds possessing antidepressant effects (e.g., imipramine, maprotiline and fluoxetine) attenuate the reduction in DVoc rates during the depression-like phase [8,11,12]. Common stress and depression biomarkers are present in the model and include elevated corticosterone and interleukin-6 (IL-6) levels [8,11]. As a drug screening paradigm, the chick model has outperformed traditional rodent depression models [13,14] by avoiding two false positives (e.g., memantine and antalarmin) [15] which were ineffective in clinical trials

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[16,17]. Further adding to the validity, the model displays cognitive biases in a manner parallel to those displayed in individuals presenting anxiety (i.e., more pessimism) and depressive disorders (i.e., more pessimism and less optimism) [18] the latter of which was reversed by the antidepressant imipramine [19].

Valid animal model simulations should also possess etiological homologies. Two factors associated with stress vulnerability are environmental and genetic mediators. Common environmental mediators associated with depressive episodes include abuse, neglect [20], low socioeconomic status and divorce [21], among others. Indeed, the chick anxiety–depression model has shown sensitivity to environmental manipulation [22], where chicks housed in an enriched homecage (e.g., perches, grit, mirrors and string) displayed a delayed onset of behavioral despair to the isolation stressor compared to chicks housed in standard caging. These findings are consistent with environmental enrichment delaying the onset of behavior despair in rodent models [23,24].

One genetic mediator associated with depression in humans includes polymorphisms (one or two copies of the short (S) allele) of the 5HTT gene [25,26]. Two approaches to studying genetic mediators to stress vulnerability in rodent models of depression are using selective inbred lines (e.g., Flinders Sensitive Line) [27,28] and gene knockout models (e.g., 5-HTT knockout lines) [29,30]. Selective breeding in chickens also yield variations in emotionality [31], stress responsivity and biological mechanisms [32]. For example, differences in feeding, comforting behaviors, adrenal gland size, corticosterone, 5-HT levels and 5-HT1A receptor expression between strains selected for varying commercial productivity and survivability following transportation stress [32].

The existing literature validating the chick anxiety–depression model was derived from a single white leghorn strain [33]. However, a wide variety of chick strains are available to explore stress vulnerability in this neuropsychiatric simulation. The ability to identify a stress-vulnerable (and possibly resilient) strain would provide yet another homology between the chick anxiety–depression model and the clinical syndrome. Moreover, such work could then afford the exploration of complex interactions between gene and environmental mediators that mitigate stress vulnerability and/or responsivity to pharmacological treatment.

2. Methods

2.1. Subjects and housing characteristics

Nine different strains of cockerels (*Gallus gallus*, Ideal Poultry Cameron, TX, USA) were received 2 days post hatch and housed in a 34 × 57 × 40 cm stainless steel cages with 12–13 chicks per cage. Strains were selected on the basis of feather pigmentation diversity and hatch availability within the time parameters of this study. Pigmentation [34] and associated genes [35] have been shown related to physiological and behavioral differences in aves, and include aggressiveness [35,36] and exploratory and social behaviors [35]. The strains included were Ameraucana, Barred Rock, Black Australorp, Buff, White Leghorn 236, New Hampshire Red, Production Red, Rhode Island Red and Silver Laced Wyandotte. Food (Purina Start and Grow, St Louis, Missouri, USA) and water was available ad libitum through one quart gravity-fed feeders (Murray MacMurray; Model 4BGFJ) and waterers (Murray MacMurray; Model 4YQW0). Room temperature was maintained at 29 ± 1 °C and overhead illumination was maintained on a 12-h light–dark cycle (7 am–7 pm).

2.2. Isolation apparatus

A six-unit test apparatus containing Plexiglas viewing chambers (25 × 25 × 22 cm) situated in sound-attenuating enclosures was used to collect isolation-induced distress vocalizations. The units were illuminated using 25 W light bulbs and ventilated by an 8-cm diameter rotary fan (Model FP-108AXS1; Commonwealth Industrial Corp. Taipei, Taiwan). Miniature video cameras (Model PC60XP; SuperCircuits, Inc., Liberty Hill, Texas, USA) mounted at floor level in the corner of the enclosures and routed through a multiplexer (Model PC47MC; SuperCircuits, Inc.) allowed for animal observation. Distress vocalizations were collected via microphones [Model 3-675-001 (modified for AC current); Lafayette Instruments, Lafayette, Indiana, USA] mounted on the ceiling of the Plexiglas chamber and routed through a USB interface via custom-designed software.

2.3. Procedure

Three strains were tested per session over three consecutive weeks. At ages 5–6 days post hatch, the chicks were removed from their home-cage, color-coded with a felt marker and weighed to identify potential outliers (i.e., low weights). The chicks were then placed into the isolation apparatus alone (isolated condition) or with two conspecifics and two 20.3 × 20.3 cm mirrors positioned alongside the walls (non-isolated condition). Distress vocalizations were recorded for 90 min; however, due to software collection error the test session ended at 89 min. Therefore, the depression-like phase constituted the last 59 min of the test session rather than 60 min. The animals were tested once and returned to their home cage following these experimental procedures. The chicks that served as conspecifics were used twice for the two squads that constituted the non-isolated condition. These protocols were approved by the University of Mississippi's Institutional Animal Care and Use Committee (protocol no. 11-013).

2.4. Dependent measures

DVocs were transformed into a rate/min function and collapsed across 3-min blocks before analyses. Separate ANOVAs (1- and 2-way) were conducted to examine the effects of isolation condition and isolation time for each strain. In order to assess the differences of onset of the depression-like phase, we calculated the time point at which each chick's DVoc rate/min from the anxiety-like phase (0–3 min) had declined by 25, 50, 75 and 95% to the rate/min of the depression-like phase (30–89 min). To elaborate, DVoc rates were compared minute by minute over consecutive 3-min blocks to determine the time point at which the average rate of that block was at or below these four thresholds; the middle time point of that block was operationally defined as the onset latency into 25, 50, 75 or 95% of the depression-like phase.

3. Results

The effects of social separation stress on DVoc rates for each strain are presented in Fig. 1, panels A–I. In general, chicks in the non-isolated condition displayed fewer DVocs than isolated chicks throughout the test session. Several strains (e.g., Ameraucana, Black Australorp and New Hampshire Red) displayed unexpectedly higher DVocs (e.g., 35–80/3-min block) in this treatment condition which rapidly declined to comparable rates of other strains within 15–30 min of the test session. In contrast, chicks in the isolated condition initially displayed relatively high DVocs (>100/3-min block) which declined within 20 min to approximately 50% of the initial rate and remained stable thereafter. Consistent with these observations, 2-way between–within ANOVAs revealed significant main effects of isolation condition for each strain, $F(1,638) = 51.60–168.32$, $ps < 0.0001$, significant main effects of test session time for each strain $F(29,638)$, 2.66–10.03, $ps < 0.0001$, and significant isolation × time interaction for all but one (i.e., New Hampshire Red) strain $F(29,638)$, 1.17–4.78, $ps < 0.0001$.

To illustrate differences in DVoc rate between the anxiety-like (0–3 min) and the depression-like phase (30–89 min), paired *t*-tests were conducted for each strain in the isolated condition. For each strain, a significant decrease in mean DVoc rate/min was observed between the phases, $ts(11) = 4.85–10.67$, $ps < 0.0005$.