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Pharmacological reversal of cognitive bias in the chick anxiety-depression model

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ABSTRACT

Cognitive bias presents in clinical populations where anxious individuals adopt a more pessimistic interpretation of ambiguous aversive stimuli and depressed individuals adopt both a more pessimistic interpretation of ambiguous aversive stimuli and a less optimistic interpretation of ambiguous appetitive stimuli. These biases have been reversed by anxiolytics and antidepressants. In the current study, chicks exposed to an isolation stressor of 5-min to induce an anxiety-like state or 60-min to induce a depressive-like state were tested in a straight alley maze to a series of morphed ambiguous appetitive (chick silhouette) to aversive (owl silhouette) cues. Chicks in the depression-like state displayed more pessimistic-like and less optimistic-like approach behavior to ambiguous aversive and appetitive cues, respectively. Both forms of cognitive bias were reversed by 15.0 mg/kg imipramine. Chicks in anxiety-like state displayed more pessimistic-like approach behavior under the ambiguous aversive stimulus cues. However, 0.10 mg/kg clonidine produced modest sedation and thus, was ineffective at reversing this bias. The observation that cognitive biases of more pessimism and less optimism can be reversed in the depression-like phase by imipramine adds to the validity of the chick anxiety–depression model as a neuropsychiatric simulation.

This article is part of a Special Issue entitled 'Anxiety and Depression'.

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 (Davidson and Connor, 2004; Krishnan, 2004; Nelson, 2004; Rosenbaum and Tollefson, 2004). Advancements in novel pharmacotherapies for psychiatric disorders rely, in part, on the development, validation and utilization of animal model simulations. While the elevated plus maze and the forced swim test, are common models of anxiety and depression in behavioral pharmacology, respectively, they are not without problems. (Frazer and Morilak, 2005; Kalueff and Tuohimaa, 2004; Kalueff et al., 2007).

The chick anxiety–depression model (Sufka et al., 2006), which simulates both clinical syndromes within a single paradigm, may be a useful adjuvant to traditional models. The procedure involves a social separation stress that initially produces high distress vocalization (DVoc) rates characteristic of an anxiety-like state (i.e., panic model; Panksepp et al., 1978, 1980; Warnick et al., 2006) that is followed by lower DVoc rates characteristic of a depression-like state (i.e., behavioral despair model; Lehr, 1989). These phases can be 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 (Sufka et al., 2006; Warnick et al., 2009; see also Lehr, 1989). Additionally, common stress and depression biomarkers are present in the model and include elevated corticosterone and interleukin-6 (IL-6) levels (Sufka et al., 2006; Warnick et al., 2009). Further, the chick model has outperformed traditional depression models by avoiding two false positives (memantine and antalarmin) (Sufka et al., 2009) which were initially detected as efficacious in rodent screening assays (Nielsen et al., 2004; Kos and Popik, 2005) but not in clinical populations (Zarate et al., 2006; Schechter et al., 2005).

The validity of any animal model simulation is based on how well that model fits the human clinical syndrome in terms of etiology, symptomatology, pathophysiology and response to treatments (van der Staay, 2006). One clinical feature of anxiety and depressive disorders is a disturbance in cognition called cognitive

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bias. More specifically, anxious individuals make more pessimistic judgments of ambiguous stimuli; depressed individuals not only make more pessimistic judgments of ambiguous stimuli, but also make less optimistic judgments of ambiguous stimuli (Wright and Bower, 1992; MacLeod and Byrne, 1996; Miranda and Mennin, 2007). Cognitive bias is observed on a wide variety of tasks that include interference tasks (e.g., a modified version of the Stroop Task), attentional probe tasks and homophone tasks, among others (for review see, Mathews and MacLeod, 1994; Mogg et al., 2006; Mogg and Bradley, 2005).

Recent research has demonstrated cognitive bias in the chick anxiety–depression model (Salmeto et al., 2011). Chicks exposed to an isolation stressor of 5-min to induce an anxiety-like state or 60-min to induce a depressive-like state were then tested in a straight alley maze to a series of morphed ambiguous appetitive (chick silhouette) to aversive (owl silhouette) cues. In non-isolated controls, runway start and goal latencies generally increased as a function of greater amounts of aversive characteristics in the cues. In chicks in the anxiety-like state, runway start latencies increased to ambiguous aversive cues, reflecting more pessimistic-like behavior. In chicks in the depression-like state, runway start latencies increased to both aversive and appetitive ambiguous cues, reflecting more pessimistic-like and less optimistic-like behavior, respectively. The observation that cognitive biases in the chick anxiety–depression model are homologous to that of the human clinical syndromes adds an important validation step of the model as a neuropsychiatric simulation.

Several studies in clinical populations have shown cognitive bias reversed by various antidepressant drug classes. Anxious individuals given a serotonin selective reuptake inhibitor (SSRI) showed a reversal of negative interpretation bias on threat-related cues (i.e., more pessimism) on the modified Stroop Task (Weinstein and Nutt, 1995) and on the homophone task (Mogg et al., 2004). Depressed individuals given a norepinephrine selective reuptake inhibitor (NSRI) showed a reversal of decreased ability to recognize happy expressions (i.e., less optimism) on a facial recognition task and a reversal of negative bias to positive self-referential characteristics on an emotional categorization and memory task (Harmer et al., 2009). Interestingly, in anxious individuals, benzodiazepine (BZ) anxiolytics do not affect cognitive bias on the modified Stroop Task. This has been attributed to cognitive slowing that accompanies BZ receptor agonism (Golombok et al., 1991; Stewart et al., 2000).

The present research sought to determine whether the patterns of cognitive bias in the chick anxiety–depression model are similarly sensitive to pharmacological reversal. If such a homology exists, antidepressant administration should a) reverse more pessimistic-like behavior under ambiguous aversive cues in both anxiety-like and depression-like states and b) reverse less optimistic-like behavior under ambiguous appetitive cues in the depression-like state. It is also possible that a non-benzodiazepine anxiolytic may reverse more pessimistic-like behavior in the anxiety-like state. Such findings would further validate the chick anxiety–depression model as a neuropsychiatric simulation.

2. Methods

2.1. Subjects and housing characteristics

Cockerels (Gallus gallus; W36; Cal-Maine Foods, Inc., Mendenhall, Mississippi, USA) were received 1-day post hatch and housed in 34 × 57 × 40 cm stainless steel cages with 12–13 chicks per cage. Chicks were removed and briefly handled daily to minimize experimenter-related stress. 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. Apparatus

2.2.1. Straight alley maze

The apparatus consisted of a 50 × 30 × 10 cm arena made of opaque high-density polyethylene material that contained a straight alley maze adjacent to a holding arena (see Salmeto et al., 2011 for full description). Briefly, the maze consisted of a 10 × 10 cm start box with a guillotine door that opens up to a 40 × 10 cm runway with either an 8 × 10 cm mirror or various 8 × 10 cm stimulus cues placed at its end. A 40 × 20 cm holding arena housed 12 conspecifics throughout the test session and permitted the testing of chicks under non-isolated treatment conditions. These conspecifics remained out of view during maze testing. However, once chicks reach the goal, full view of the arena was permitted through a 20 × 10 cm clear Plexiglas wall. Pine bedding was placed throughout the arena floor and food and water was available ad libitum in 200 ml stainless steel cups.

2.2.2. Morphed stimulus conditions

Morpheus Photo Morpher v3.01 Professional for Mac (Morpheus Software, LLC) was used to produce 'morphed' images that blended elements of a chick and a horned owl silhouette by mapping a series of approximately 200 dots onto each photos to match the location of the dots between the images. This allowed for 100 morphed frames linking the start (chick) and end (owl) photos. Within this series two key frames were defined: 75% chick and 25% owl, and 25% chick and 75% owl were used (75c:25o and 25c:75o). The pixilated edges of the images were smoothed out and the images were adjusted so that they were all approximately the same size and fit on an 8 × 10 cm stimulus card. The images were saved as jpeg files, printed and placed behind a clear glass plate during testing (see Salmeto et al., 2011 for pictures of morphed stimuli).

2.2.3. 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; Rodale, Great River, New York, USA). Miniature video cameras (Model PC60XP; Super Circuit, Liberty Hill, Texas, USA) mounted at floor level in the corner of the enclosures and routed through a multiplexer (Model PC47MC; Super Circuit) allowed for animal observation. Distress vocalizations were collected via microphones [Model 3-675-001 (modified); Lafayette Instruments, Lafayette, Indiana, USA] mounted on the rear wall of the Plexiglas chamber, routed through sound-activating relays (Model 630400A; Lafayette Instruments; settings: 60–75% sensitivity, 0.10-s delay) and collected a USB interface via custom-designed software.

2.3. Pilot study

The notion that anxiolytic sedative effects could confound runway performance, a pilot study determined optimal dosing for clonidine and imipramine under non-isolated test conditions. The pilot study revealed one unexpected outcome: exposure to the test protocol in non-isolated groups led to modest but measurable and pharmacologically dissociable stress behaviors on DVocs and runway performance under ambiguous stimulus cues. This stress effect is likely due to experimenter exposure, weighing and injection procedures, apparatus novelty and flock reduction associated with the test protocol (Feltenstein et al., 2002). These findings prompted the use of a no-test group (i.e., no exposure to isolation test apparatus prior to maze testing) to serve as the control for the experiment.

2.4. Procedure

This experiment was conducted to test whether cognitive bias could be reversed under an anxiety-like and a depression-like state. In the first trial, at age 4 days post hatch, 12 cagemate conspecifics were placed into the holding arena and individually tested in the maze under the mirror cue condition. Each chick was placed into the start box for 15-s after which the guillotine door was raised. Dependent measures were start and goal latency and farthest distance traveled. Start latency was defined as the time it took to step completely outside the start box. Because all test sessions were terminated at 5-min, the farthest distance traveled (cm) from the start box was measured to account for possible differences between chicks that complete the maze and those that did not. Chicks were placed back into the holding arena until all were tested. Group assignment for Trial 2 was based on goal latency performance in Trial 1.

In the second trial, at either 5 or 6 days post hatch, chicks were administered either 0.10 mg/kg clonidine (tested for 5-min), 15.0 mg/kg imipramine (tested for 60-min), a physiological saline (tested for 5-min), and a physiological saline (tested for 60-min). All chicks were injected with drug probes 15-min prior to testing. Following apparatus testing, chicks were transported from the isolation apparatus in a 2-quart opaque plastic container and tested immediately in the maze under one of four stimulus cue conditions: mirror, 75c:25o morph, 25c:75o morph: or 0c:100o (owl silhouette). To assess a baseline for each stimulus cue, a no-isolation test control group was administered physiological saline and tested immediately within the maze. In addition, these chicks remained in the arena throughout the test