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Antisocial and seizure susceptibility phenotypes in an animal model of epilepsy are normalized by impairment of brain corticotropin-releasing factor

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Abstract

Social interaction phenotyping is an unexplored niche in animal modeling of epilepsy despite the sensitivity of affiliative behaviors to emotionality and stress, which are known seizure triggers. Thus, the present studies examined the social phenotype of seizure-susceptible El and nonsusceptible ddY strains both in untreated animals and following preexposure to a handling stressor. The second aim of the present studies was to evaluate the dependence of sociability in El mice on the proconvulsive, stress neuropeptide corticotropin-releasing factor (CRF) using CRF–SAP, a conjugate of CRF and the toxin saporin, which selectively reduced CRF peptide levels in the basolateral amygdala of El mice. El mice exhibited lower social investigation times than ddY counterparts, whereas central administration of CRF–SAP normalized social investigation times relative to ddY controls. Moreover, handling-induced seizures in El mice were reduced by 50% following treatment with CRF–SAP relative to saporin alone-injected El controls. The results of this study suggest that tonically activated CRF systems in the El mouse brain suppress affiliative behavior and facilitate evoked seizures.

Keywords: Social interaction; Epilepsy; Stress; Corticotropin-releasing factor; Seizure; Tail suspension handling

1. Introduction

Preclinical evidence suggests an inverse relationship between social interaction and seizure susceptibility. For example, seizure-susceptible El dams exhibit social withdrawal and neglect in caring for offspring [1], and an increase in the quality of dam–pup social interaction by cross-fostering attenuates seizure susceptibility [2]. Similarly, juvenile recognition, an innate form of short-term working memory, is also reported to be deficient in seizure-susceptible El mice of both genders [3]. Consistent with these findings from the animal literature, changes in sexuality and aggressivity associated with human epilepsy provide evidence of strain in interpersonal relations [4]. A second rationale for suspecting that an inverse relationship exists between social status and seizure outcome is the ability of stressor exposure to modulate these states in opposing directions. In organisms with a predisposition for epilepsy, early-life stress and traumatic events are associated with an increase in occurrence of seizures [5]. Moreover, daily emotional stressors and excess environmental stimulation precipitate seizures in humans with epilepsy [6]. Both the development of the disorder and the repeated occurrence of seizures are facilitated by environmental stressors [7]. The co-occurrence of social deficits, seizure susceptibility and altered stress reactivity implicates the proconvulsive neuromodulator corticotropin-releasing factor (CRF), which acts as an anxiogenic agent in the brain to suppress social interaction [8]. In addition, CRF receptor antagonists exert complementary prosocial and seizure-protective actions [9–12]. Moreover, central administration of a CRF receptor agonist promotes locomotor activation [13], which is one functional phenotype of the seizure-susceptible El mouse [14]. Thus, available evidence

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suggests that normal social interaction is impaired in seizure-prone organisms and that centrally mediated stress-coping responses may modulate the severity of these psychosocial and neurological deficits.

The present studies examined social interaction among seizure-resistant ddY and seizure-susceptible El mice as a potential common index of emotionality and seizure susceptibility. Accordingly, the first experiment examined strain differences in spontaneous social investigation of El and ddY mice placed in an unfamiliar environment. Social interaction was measured among same-gender, but unfamiliar, adult rodents by recording the amount of time an experimental animal engaged in olfactory investigation of a nonexperimental stimulus animal while present in a cage together [15]. Decreased social interaction time in the absence of locomotor or sensory impairments indicates a high level of emotionality [16]. The second experiment examined how exposure to a tail suspension handling stressor, a seizure trigger in El mice [17], prior to the social investigation test affected performance when an unfamiliar intruder mouse was introduced into the home cage environment of an experimental mouse. These experiments tested the hypothesis that seizure-susceptible El mice would exhibit a general, anxiogenic-like decrease in social investigation relative to ddY controls. Because of the close association between stress responsivity and seizure induction, the present studies also tested the hypothesis that brain CRF activation plays a role in modulating the social phenotype and handling-induced seizure susceptibility of El mice. The specific hypothesis under test was that higher reactivity to CRF in El mice relative to normal ddY controls would promote enhanced sensitivity to environmental stressors in both social interaction and seizure susceptibility testing contexts. To investigate this hypothesis, El mice were administered CRF–SAP, which is a conjugate of CRF and the neurotoxin saporin [18]. When injected intercranially, CRF–SAP binds to CRF receptors in affected brain regions, where the saporin protein inactivates these receptor-bearing neurons for a period of at least 2 weeks [18]. Note that CRF type 1 receptor-bearing neurons are impacted preferentially by CRF–SAP treatment, whereas other components of the brain CRF system, including CRF type 2-bearing neurons, remain relatively unimpaired [18]. Thus, the present studies tested the hypothesis that El mice injected with CRF–SAP would perform normally in a social interaction task and also experience a lessening of seizure frequency. Because brain CRF activation also promotes negative energy balance [19], body weight change and posttreatment plasma glucose levels were also recorded in the present studies as indices of a potential nonspecific bioenergetic mechanism of CRF–SAP action.

2. Methods

A total of 96 El and 40 ddY mice were used in the present study as experimental and nonexperimental stimulus subjects. All mice were group housed by default in a reverse light–dark cycle colony (lights off at 10:00, lights on at 22:00) at 21 °C and 48% humidity. All procedures were performed during the dark phase of the circadian cycle, when mice are awake and active. Water and standard lab chow (ProLab3000, LabDiets, Richmond, IN, USA) were available ad libitum throughout all experiments. The Institutional Animal Care and Use Committee of Boston College approved all experimental procedures described herein.

2.1. Experiment 1: Assessment of the social interaction phenotype of ddY and El mice

2.1.1. Animals

A total of 32 mice were employed in Experiment 1. Experimental El ($n = 8$) and ddY ($n = 8$) mice and a matching number ($n = 8$/group) of nonexperimental stimulus mice of each strain were employed in the social interaction test. Groups were composed of male and female mice in equal 50:50 ratios. The stimulus mice were housed singly 24 hours prior to data collection, and on cage transfer, some of the soiled bedding from the home cage was transferred into each new cage to facilitate environmental acclimation. All mice were at least 120 days old at the time of testing.

2.1.2. Social interaction test

All experimental and stimulus mice were moved to a testing room separate from the colony 15 minutes before the start of social interaction testing. The experimental mouse was placed gently in the home cage of a stimulus mouse of the same gender and strain. The experimental mouse's social behavior, specifically olfactory investigation of the home cage mouse, was recorded using a video camera during a 5-minute social interaction test. Stimulus animals were marked with black stripes using a nontoxic marker before the test to distinguish them from the experimental subjects. The mice were tested in random order, and social behavior was scored by treatment-blind observers. The social interaction phenotyping experiment was replicated twice using separate naïve groups of mice, and the results were pooled.

2.2. Experiment 2: Impact of seizure susceptibility testing on social investigation

2.2.1. Animals

Experimental and nonexperimental stimulus mice were selected as in Experiment 1, except that only El strain mice were used in this experiment. A total of 64 El mice were employed in Experiment 2. Experimental (8 of each gender) and control (9 males and 7 females) mice were singly housed (with bedding from their original group home cage) starting 24 hours before testing. Gender-matched nonexperimental stimulus mice ($n = 32$) remained in group housing. All mice were at least 120 days old at the time of testing.

2.2.2. Tail suspension handling

Each mouse was picked up by the tail and suspended in the air 10–15 cm above the floor of its home cage for 30 seconds and then placed in a clean cage for 2 minutes, during which time they could roam about freely. The mouse was then suspended for an additional 15 seconds before it was returned to its home cage. No seizures were elicited in El mice by this handling procedure. Mice in the control group were not handled. After a 30-minute delay, a stimulus mouse was introduced into each experimental mouse home cage. The social investigation behavior of the experimental mouse was recorded using a video camera during the 5-minute social interaction test. Stimulus animals were marked with black stripes using a nontoxic marker before the test to distinguish them from the experimental subjects. Mice were tested in random order, and social behavior was scored by treatment-blind observers. The handling-induced social phenotyping experiment was replicated twice using separate naïve groups of mice, and the results were pooled.