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Anxiogenic effects of brief swim stress are sensitive to stress history

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ABSTRACT

Stressors that are controllable not only protect an individual from the acute consequences of the stressor, but also the consequences of stressors that occur later. This phenomenon, termed "behavioral immunization", is studied in the rat by first administering tailshocks each of which can be terminated (escapable tailshock) by an instrumental wheel-turn response prior to exposure to a second stressor. Previous research has shown that exposure to escapable tailshock blocks the neurochemical and behavioral consequences of later inescapable tailshock or social defeat stress. Here we explored the generality of behavioral immunization by examining the impact of prior escapable tailshock on the behavioral consequences of cold swim stress. Exposure to a 5 min cold-water (19 °C) swim caused an anxiety-like reduction in social interaction that was dependent upon 5-HT_{2C} receptor activation. Rats with prior exposure to escapable tailshock did not develop the swim-induced anxiety. Plasticity in the medial prefrontal cortex, a hypothetical neural mechanism underlying behavioral immunization, is discussed.

1. Introduction

There is enormous variability in how individuals respond to stressors and whether the stressor episode will interact with the development of psychiatric disorders (Alleva and Francia, 2009; Dudley et al., 2011; Franklin et al., 2012). Although it is clear that stress history is an important modulating factor, the features of prior experience that are critical remain largely unknown. Often, prior exposure to a stressor or adverse circumstance increases the behavioral or neurochemical impact of a subsequent stressor, particularly if the prior stressor is intense and different from the later target stressor (Girotti et al., 2011; Johnson et al., 2002; Pelton et al., 1997). Until recently, the emphasis has been on attempting to determine the mechanisms by which prior experiences produce such potentiation. However, there are circumstances under which prior stress experience blunts the impact of subsequent stressors (Lyons and Macri, 2011), and there has been an increasing interest in understanding the processes that underlie "resilience" (Dudley et al., 2011; Russo et al., 2012; Southwick and Charney, 2012).

The degree of behavioral control that the organism is able to exert over the stressor is arguably the most potent experiential aspect of the stressor episode that modulates its influence on behavioral and neurochemical reactions to subsequent stressors (Cabib et al., 2012; Southwick and Charney, 2012; Southwick et al., 2005). The presence of behavioral control (the ability to alter the duration, intensity, temporal pattern, etc. of an adverse event by means of behavioral responses) not only blunts the impact of the stressor being experienced, but also potently reduces the behavioral impact of subsequent uncontrollable stressors. Exposure to intense stressors, such as social defeat or inescapable tailshocks, produces a constellation of behavioral changes that include both anxiety-like (e.g., reduced social investigation) and depressive-like (e.g., anhedonia) elements (Maier and Watkins, 2005; Overstreet, 2012). These behavioral effects are mediated, at least in part, by changes in dorsal raphe nucleus (DRN) 5-HT neurons that are consequent to the intense activation of these neurons produced by the stressor (for review see Maier and Watkins, 2005). Experience with a series of escapable tailshocks (ES) during which each tailshock can be terminated by turning a small wheel located in the front of the chamber, blocks both the anxiety and depression-like behavioral changes, as well as the 5-HT DRN activation produced by later inescapable tailshock (Amat et al., 2006), a phenomenon that has been called "behavioral immunization" (Williams and Maier, 1977). An initial experience with exactly matched inescapable tailshocks (IS) does not produce immunization, so the immunization depends on the controllability of the initial tailshocks. Strikingly, the immunizing effects of ES persist for at least 7 days, and may persist for at least a month, depending on the outcome measure (Kubala et al., 2012; Rozeske et al., 2012).

Because mechanisms of stress resistance and resilience are critically important to understanding the development of psychiatric disease (Russo et al., 2012), our laboratory has sought to identify the procedural limits of the behavioral immunization phenomenon. Although the work cited above involved administration of tailshock in different environments in the two phases of the procedure, the

Abbreviations: DRN, dorsal raphe nucleus; ES, escapable tailshock; IS, Inescapable tailshock; 5-HT, 5-hydroxytryptamine; ANOVA, analysis of variance; LSD, least significant difference; SEM, standard error of the mean; HC, home cage.

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stressors were fundamentally the same. A critical issue with regard to the immunization phenomenon concerns whether control over tailshock would afford protection against qualitatively different stressors. At present, only one experiment has been directed at this issue. Amat et al. (2010) exposed rats to social defeat 7 days after ES or IS. As above, prior ES prevented the activation of the DRN and the anxiety-like behavioral changes associated with social defeat. This finding suggests a fundamental organismic change produced by an experience with control over tailshock and here we explore the generality of this trans-stressor effect by determining whether ES would blunt the changes produced by acute swim exposure. Because our interests focus on the consequences of stressor exposure on anxiety-like behavior, we first determined whether forced swim would induce social avoidance. In the first experiment the rats were exposed to a 5 minute swim in cold 19 °C water and tested for social exploration 1 h after swim. In the second experiment the rats have received either ES, IS or no stress 7 days before the forced swim and social exploration tests. Finally, to determine if forced swim-induced anxiety depends on 5-HT_{2C} receptors, a critical mediator of anxiety in this test (Christianson et al., 2010), the rats were given the 5-HT_{2C} receptor antagonist SB242084 after the swim.

2. Materials and methods

2.1. Animals

Adult male Sprague–Dawley (Harlan, IN) rats weighing 250–300 g at the time of experimentation were used in all experiments. The rats were housed in groups of 4 in plastic cages with shaved-wood bedding and free access to food and water at all times. Lighting in the vivarium was maintained on a 12 h light/dark cycle. All behavioral experiments were conducted in the first 4 h of the light cycle and were approved by the University of Colorado Institutional Animal Care and Use Committee.

2.2. Acute swim stress

The rats were placed in a clear glass beaker (Pyrex) 45.7 cm height × 30.5 cm diameter with water filled to a depth of 30 cm. Behavior was recorded by a digital video camera for later continuous analysis of immobility, swimming and climbing according to the definitions of Detke et al. (1995). Water temperature was 19 °C or 35 °C (see experimental procedures in Section 2.6).

2.3. Social exploration test

The juvenile social exploration test was conducted exactly as described previously (Christianson et al., 2010). Briefly, the rats were transferred to a testing room and placed into individual plastic tub cages with bedding and a wire lid. After 60 min a 28(±2) day-old juvenile conspecific was introduced into the cage and exploratory behaviors (sniffing, grooming, and pinning) initiated by the adult test subject were quantified by a trained observer who was naïve to the treatment over a 3 min period.

2.4. Escapable/yoked inescapable stress

In Experiment 2, the rats were exposed to 100 trials of either controllable, escapable tailshock (ES), exactly equal uncontrollable, inescapable tailshock (IS) or no shock. This procedure was identical to that described previously (Christianson et al., 2010). In brief, the rats were placed in a plastic chamber and restrained by the tail with cloth tape. Electrodes were attached to the tail and augmented with electrolyte paste. 100 tailshocks (33 at 1 mA, 33 at 1.3 mA and 34 at 1.6 mA) were administered by a computer with Graphic State hardware and software (Coulbourn Instruments, PA) on a variable 60 s interval (range 30–90 s). Shock intensity was increased over the session to maintain response. The rats in the ES condition were able to turn a wheel in the chamber to terminate the shock. IS rats were physically yoked to an ES subject so that when the wheel turn requirement was reached, the shock was terminated for both subjects. The wheel turn requirement began with ¼ turn and increased to 4 full turns as previously described (Amat et al., 2006; Christianson et al., 2010). If an escape was not made within 30 s of shock onset the trial was automatically terminated by the computer. Then the stress rats were returned to the home cages thereafter.

2.5. Drugs

The brain penetrant and highly selective 5-HT_{2C} receptor antagonist SB242084 (Tocris) was dissolved in saline by sonication and administered i.p. at a dose of 0.25 mg/kg in a volume of 1 ml/kg. 0.25 mg/kg was chosen based on a pilot study to minimize animal usage and was slightly smaller than previously used to reverse stressor-induced anxiety (Christianson et al., 2010; Strong et al., 2009).

2.6. Experimental procedures

2.6.1. Experiment 1

The purpose of Experiment 1 was to determine the effects of a brief cold water swim on anxiety-like behavior in the social exploration test. A pilot study indicated that a 15 min swim, the duration of a typical forced swim test (Detke et al., 1995) in 19 °C water, produced a robust decrease in social exploration but was confounded by severe hypothermia. Thus, the rats have received cold swims of 0, 5, 10 or 15 min at 19 °C. In order to determine whether the cold temperature of the water is critical, a final group received a 15 min swim in 35 °C water. After 60 min a juvenile was added and social exploration tests were conducted as described above.

2.6.2. Experiment 2

The goal of Experiment 2 was to test whether pretreatment with controllable or uncontrollable stress would alter the behavioral response to swim stress and the anxiety observed 60 min later. We first conducted a time course experiment in which separate groups of rats were exposed to ES, IS or HC treatments and subsequently were given social exploration tests 1, 3 or 7 days later. IS, but not ES, reduced social exploration time 1 and 3 days after stress and all groups appeared equal by day 7. In the critical experiment, the rats were assigned to 1 of 4 groups: no stress home cage control (HC), Swim only (Swim), escapable stress and swim (ES-Swim) or inescapable stress and swim (IS-Swim). Escapable or inescapable stress occurred on experimental day 1. HC and Swim rats remained undisturbed in the vivarium. On day 7, Swim, ES-Swim and IS-Swim rats received a 5 minute swim in 19 °C and social exploration tests were conducted 60 min later as described in Experiment 1. HC rats were given social exploration tests at the same time without any prior treatment.

2.6.3. Experiment 3

The purpose of Experiment 3 was to test whether the reduction in social exploration observed 60 min after swim stress was mediated by 5-HT_{2C} receptors. This was done because reduction in social exploration produced by inescapable tailshocks and other stressors is mediated by these receptors (Christianson et al., 2010; Harvey et al., 2012; Overstreet et al., 2003, 2006). The rats were assigned to 1 of 4 treatment groups in a 2 (swim or no stress) × 2 (0 or 0.25 mg/kg SB242084) design. The rats in the swim group were exposed to a 5 min swim in 19 °C water, the minimum required to produce anxiety like behavior followed immediately by 0 or 0.25 mg/kg SB242084 i.p. Rats in the no stress group were given injections before placement into social exploration test cages. The rats were transferred to social exploration test cages and tested for anxiety like behavior 60 min after stress as in Experiment 1.