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Endocrine and immunological correlates of behaviorally identified swim stress resilient and vulnerable rats

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Abstract

Animal models of stress-induced depression have identified a bimodal reactivity to stress, namely 'resilience' and 'vulnerability.' Possible corresponding differences in endocrine and immunological responses between these groups have not been delineated. Male Sprague–Dawley rats were divided into three groups: stress ($n=25$), confined controls ($n=7$), and home cage controls ($n=7$). Stress rats were exposed to 80, 5-s inescapable cold water swim trials (15 °C). Twenty-four hours later, the stress rats were tested on an instrumental swim escape test (SET) but now they had access to an omnidirectional lever that terminated the stress. Immediately after the SET, trunk blood was collected to assay for serum corticosterone (CORT), and spleens were removed and natural killer cell activity (NKCA) and concanavalin A (CON-A) induced lymphocyte proliferation determined. Subjects in the stress treatment group were divided into distinct 'resilient' and 'vulnerable' categories by a median split for average escape latencies across the last 25 trials of the SET. Stress rats secreted more CORT than controls and vulnerable rats secreted greater levels than resilient rats. NKCA was greatest in control rats, and was decreased in the stress rats although the resilient and the vulnerable groups did not differ. Conversely, CON-A-induced lymphocyte proliferation was greatest in stress rats, vulnerable rats exhibiting more proliferation than resilient rats, but both were greater than both control groups. Stress animals were hypothermic throughout the swim stress procedures but exhibited a stress-induced fever following the initial swim trials. The observed differences may have important predictive and theoretical utility for vulnerable and resilient profiles.

Keywords: Corticosterone; Natural killer cell activity; Lymphocyte proliferation; Psychoneuroimmunology; Body temperature

1. Introduction

Stress has been proposed to play a role in the pathophysiology of depressive illness (Wong and Licinio, 2001). As a result, a number of animal models have been developed to examine this relationship. In such models, exposure to inescapable stress induces depressive symptoms that can be ameliorated with anti-depressant treatments (Porsolt et al., 1977; Sherman et al., 1982).

The two most prominent animal models of depression are the inescapable shock (IS)-induced learned helplessness (LH) (Sherman et al., 1982) and the forced swim 'behavioral despair' model (Porsolt et al., 1977). Studies investigating the effects of repeated IS in a variety of species have consistently reported the development of learning impairments when subjects are exposed to a subsequent session of shock in which escape is possible (Huang et al., 2004; Maier et al., 1973; Maier and Seligman, 1976; Petty et al., 1994; Seligman et al., 1975; Steciuk et al., 1999). These cognitive impairments are attributed to a form of learning termed 'learned helplessness' (LH), in which the animal learns in the initial shock session, having failed a number of attempts

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to escape shock, that its behavior and outcomes are independent, and consequently inhibits the natural proclivity to learn a simple escape response in the subsequent session. LH effects also include concomitant modulations in emotion, such as enhanced fear (Maier, 1990), as well as motivational deficits such that little or no effort is made to escape (Maier and Seligman, 1976). Such deficits are eliminated if animals are given control in the initial session of shock and are thus found to be a consequence of the uncontrollability associated with the shock stressor rather than the stress per se (Maier and Seligman, 1976).

The forced swim test (FST) (Porsolt et al., 1977), which has been employed to test the motivational deficits of LH, does not involve an escape test following the initial stress session (Connor et al., 1997). Instead, behavioral depression is characterized as an immobile posture (floating) during a 5-min forced swim test 24-h following a 15-min forced swim exposure (Connor et al., 1997; Porsolt et al., 1977; Weiss et al., 1998). Rats exposed to this procedure have been observed to remain immobile for 75% of the duration of the test: a state described as 'behavioral despair' (Porsolt et al., 1977). Recently, the behavior of rats in the FST has been refined and allows one to quantify both active and passive behaviors that include: immobility, swimming, and climbing (Lucki, 1997).

The proportion of animals susceptible to stress-induced behavioral depression varies according to the experimental protocol employed (Petty et al., 1994) and the strain of rat used (Wieland et al., 1986). A consistent and important finding arising from these variations, however, is that not all animals develop this depressive symptomatology following stress (Christianson and Drugan, 2005; Drugan et al., 1989b; Huang et al., 2004; Petty et al., 1994; Steciuk et al., 1999; Weiss et al., 1998). Research within the IS model of LH indicates that rats diverge into two distinct populations based on their reactivity to stress: those that do not develop LH, often termed stress 'resilient,' and those that do, termed stress 'vulnerable' (Drugan et al., 1989b, Minor et al., 1994; Petty et al., 1994). Similarly, work using the behavioral despair test has identified rats with high and low immobility in the FST (Drugan et al., 1989b; West and Weiss, 1998). These distinct patterns of behavior have also been found to be reproducible and stable over time in both the IS and behavioral despair models (Drugan et al., 1989b).

The reliance on the IS and behavioral despair paradigms is problematic for a number of reasons. For the IS model, the caveat is that shock is an aversive stimulus rarely encountered by rats and other species in a naturalistic setting, thereby limiting external validity. The results generated from this model, therefore, may be unique to the properties of shock. The behavioral despair model, on the other hand, while avoiding the nociceptive properties of shock, does not permit the assessment of the cognitive deficits induced by inescapable stress. In response to these limitations, we have recently tested rats in a more naturalistic stress paradigm, that is, intermittent cold water swim (ICWS) stress, which also permits the examination of the cognitive impairments characteristic of LH (Christianson and Drugan, 2005). To achieve this, Christianson and Drugan (2005) employed a swim stress paradigm designed by Brown et al. (2001) that allows repeated exposure to swim stress, as well as a subsequent instrumental swim escape test. The parameters of this protocol (i.e., trial number and duration, and inter-trial interval) are similar to studies employing shock as the stress-induction procedure, thereby allowing an indirect comparison to results within the IS model.

Studies within the IS paradigm have attempted to identify the physiological and behavioral mediators of resilience and vulnerability (Drugan et al., 1989a, 1993; Minor et al., 1994; Minor and Hunter, 2002; Petty et al., 1994; Sherman and Petty, 1980). There is, however, a paucity of research investigating the endocrine and immunological consequences of these divergent behavioral responses. Vulnerable rats have been demonstrated to have a significantly lower elevation in serum corticosterone (CORT) levels than resilient rats following exposure to the shock escape task (Chover-Gonzalez et al., 1999, 2000). In contrast, enhanced c-Fos-like immunoreactivity was found in the hypothalamic paraventricular nucleus of LH animals suggesting enhanced activity and consequent HPA axis overactivity (Huang et al., 2004). These contradictory findings warrant further examination of differences in CORT between vulnerable and resilient animals.

It is likely that the differences in the stress response between resilient and vulnerable animals will result in corresponding changes in immune system function, given the well-documented interactions between the neuroendocrine systems activated during stress and immune function (Dantzer and Kelley, 1989; Maier and Watkins, 1998). Stress has traditionally been thought to be globally immunosuppressive (Graham, 1990), though this view has been challenged by animal and human investigations reporting an enhancement of some aspects of immune function following acute stressor exposure (Dhabhar, 2002; Dhabhar and McEwen, 1996; Wood et al., 1993).

Examples of stress-induced immunoenhancement reported in the research literature include the potentiated release of proinflammatory cytokines (Fleshner et al., 1998) and the release of antigen presenting cell products such as nitric oxide (Coussons-Read et al., 1994). Immunosuppressive effects of stress have also been documented, including reduced T- and B-cell counts (Connor et al., 1997) and a consistent finding of reduced natural killer cell activity/cytotoxicity (NKCA) (Ben-Eliyahu et al., 1990; Irwin et al., 1990; Shavit et al., 1984; Shimizu et al., 1996). When lymphocyte proliferation is the immunological endpoint of interest, results are ambiguous with both suppressive (Kusnecov and Rabin, 1993; Saperstein et al., 1992) and enhancing (Connor et al., 1997; Lysle et al., 1990; Shurin et al., 1994) effects being reported. The apparent inconsistency in the immunological consequences of stress are proposed to be due to the fact that changes in immune function are dependent on a number of factors, including the type of