

The influence of gender and the estrous cycle on learned helplessness in the rat

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Abstract

Although the etiology of clinical depression is unknown, women are more likely to suffer from major depressive disorder than men. In addition, in some women, there is a clear association between depression and specific phases of the menstrual cycle. Surprisingly little research has examined gender differences and the influences of the estrous cycle in this and other animal behavioral models of clinical depression. Learned helplessness is a valid animal model of stress-induced behavioral depression in which prior exposure to inescapable stress produces deficits in escape testing. Learned helplessness was studied in rats using an inescapable tail shock stress followed by a shuttle box test to determine escape latencies. Animals with mean escape latencies of ≥ 20 s after shuttle-box testing are defined as learned helpless. Males and normal cycling female rats in the estrus and diestrus II phases were studied. Female rats in the diestrus II phase had significantly higher escape latencies and exhibited a more helpless behavior than female rats in the estrus phase. Male rat escape latencies were intermediate between the two female phases. These results suggest a role for gonadal hormones in the development of stress-induced behavioral depression or 'learned helplessness.' © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Major depressive disorder disproportionately affects women at about twice the rate as compared to men (Kessler et al., 1993; Weissman et al., 1993; Williams et al., 1995). Several lines of evidence support the theory that gonadal hormones and/or their changing levels contribute to the greater incidence of major depression in women. For example, the prevalence of major depression is similar in males and females until menarche, at which time the incidence in women doubles (Angold and Worthman, 1993; Kessler et al., 1993) and this difference narrows after menopause (Hale and Cochran, 1983). Furthermore, over a third of women with major depressive disorder report premenstrual increases in depressive symptomatology (Endicott, 1993; Kornstein et al., 1995; Yonkers, and White, 1992). Finally, there are mood disorders specific to the female reproductive cycle, such as premenstrual dysphoric disorder and postpartum depression or psychosis. In fact, a subset of women with premenstrual dysphoric disorder, a mood disorder with some similarities to depression, are differentially sensitive to mood-altering effects of gonadal steroids (Schmidt et al., 1998). Despite the abundance of literature on depression and the menstrual cycle, the development and use of an animal model to investigate depressive behavior and gonadal hormones is scarce. We propose the use of the learned helplessness paradigm to test the effects of gonadal hormones on depressive behavior.

Learned helplessness is a valid animal model of stress-induced behavioral depression in which prior exposure to inescapable stress produces deficits in escape testing (McKinney, 1988; Willner, 1991). The learned helplessness model offers an opportunity to understand the behavioral and neurochemical correlates of clinical depression. Although learned helplessness is an established animal model for clinical depression, and has been investigated for over 30 years, to our knowledge, only one study to date has studied female animals using a learned helplessness paradigm. Steenbergen et al. (1989) found that female rats display less behavioral depression and more locomotor activity than male rats. Gender differences in other models of stress related to depression have also been reported. In the open field test, female rats are more sensitive to a repeated stress procedure than male rats while male rats are more sensitive to a single restraint stress than female rats (Kennett et al., 1986). In the forced swim test, male rats have a higher duration of immobility than female rats (Alonso et al., 1991).

Despite studies of sex differences and depressive behavior, few studies have investigated the influence of the estrous cycle on animal behavioral analogs of depression (Alonso et al., 1991; Marvan et al., 1996). Briefly, female rats have multiple cycles throughout a year (once every 4–5 days). For clarity, the term ‘estrous’ defines the cycle whereas the term ‘estrus’ defines a stage within the cycle. The estrous cycle of rodents consists of: (1) proestrus in which luteinizing hormone (LH), follicle stimulating hormone (FSH), estrogen and progesterone levels peak, (2) estrus in which estrogen levels are falling, progesterone levels are moderate, and LH and FSH levels are high, (3) diestrus I (metestrus) in which LH levels fall, and (4) diestrus II in which estrogen levels begin to rise (Shors, 1998; Freeman, 1994; Butcher et al., 1974).

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