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## Effect of prenatal stress and gonadal hormone condition on depressive behaviors of female and male rats

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### Abstract

Whether prenatal stress (PNS) and gonadal hormones may influence depressive behavior of rats in the forced swim test was investigated. In Experiment 1, adult diestrous female rats had increased immobility, which is indicative of depression, but did not show any significant difference in the duration of struggling compared to intact adult males. In Experiment 2, the behavior of adult intact, castrated, or castrated dihydrotestosterone (DHT)- or estrogen (E<sub>2</sub>)-replaced offspring of dams that were restrained under lights for 45 min on gestational day 18 (PNS) or were not subjected to gestational stress (non-PNS, control condition) were compared. There were no effects of PNS, but DHT and E<sub>2</sub> produced anti-depressant effects on behavior of male rats. Castration decreased struggling and increased immobility compared to intact rats. DHT or E<sub>2</sub> replacement was able to partially reinstate struggling and immobility behavior but not to levels of intact males. In Experiment 3, behavior of PNS or control rats that were in proestrus or were ovariectomized and DHT, E<sub>2</sub>, or vehicle-replaced were compared. Ovariectomy decreased struggling and increased immobility compared to that of proestrous rats. E<sub>2</sub> or DHT to control females increased anti-depressant struggling behavior compared to ovariectomized control or PNS rats administered vehicle, which demonstrated greater duration of struggling than did E<sub>2</sub>-primed, PNS rats. E<sub>2</sub> or DHT administration decreased immobility of PNS and control females. These findings suggest that E<sub>2</sub> and DHT have some anti-depressant effects but that modest PNS may alter E<sub>2</sub>'s ability to alleviate some depressive behavior in female, but not male rats.

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People and animals exposed to gestational stress demonstrate similar patterns of behavioral depression. Depressive disorders among people are characterized by symptoms of persistent anxiety, helplessness, and social withdrawal. Animals that are exposed to prenatal stress (PNS) exhibit less exploration, more freezing, and show more anxiety behavior in novel environments than do animals not exposed to gestational stress (Drago et al., 1999; Morgan et al., 1999; Pohorecky and Roberts 1991; Poltyrev, et al., 1996; Schneider, 1992; Takahashi et al., 1992; Thompson, 1957; Vallee et al., 1997; Wakshlak and Weinstock, 1990; reviewed in

Weinstock, 2001). PNS animals demonstrate social withdrawal; young PNS rats and monkeys engage in less play behavior compared to their non-stressed counterparts (Clarke and Schneider, 1993). Children exposed to PNS (psychological stress or perinatal birth complications) have poorer social interactions than do their peers (Meijer, 1985; Offord and Cross, 1969). The offspring of mothers exposed to stress during pregnancy may have an increased incidence of depressive symptomology (Huttunen and Niskanen, 1978; Watson, et al., 1999); however, those with affected offspring may be more likely to attribute such effects to stressors during pregnancy.

There are similar patterns of physiological arousal associated with PNS and depression. Prenatally stressed animals have increased levels of plasma glucocorticoids. Basal levels of corticosterone, in PNS rats (Fride, et al., 1986; Peters,

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1982; Ward et al., 2000), and cortisol, in PNS monkeys (Clarke et al., 1994), are greater compared to non-stressed controls. PNS rats have a phase shift in the circadian rhythm of corticosterone secretion (Koehl et al., 1999). Animals exposed to gestational stress also have elevated levels and/or duration of corticosterone secretion following stress than do non-PNS animals (Barbazanges et al., 1996; Henry et al., 1994; McCormick et al., 1995; Peters, 1982; Vallee et al., 1997; Weinstock et al., 1992). There is also evidence that people exposed to PNS have increased hypothalamic-pituitary-adrenal (HPA) axis function, as demonstrated by higher resting levels of plasma cortisol (Weinstein et al., 1999). Depression among people is characterized by hyperactivity of the HPA axis (Arborelius et al., 1999; Heim et al., 2000; Nemeroff et al., 1984). Depressed individuals have higher basal and stress-induced levels of cortisol and ACTH (Heim et al., 2000; Holsboer et al., 1994) and also demonstrate a phase shift in their diurnal pattern of cortisol secretion (Goodwin et al., 1982). Due to these similarities, and others, PNS has been utilized as an animal model of depression (Dugovic et al., 1999; Weinstock, 2000).

Findings from animal research suggest that PNS affects males and females differently. When compared to controls, female PNS rats have impaired learning on the Morris Water Maze (Meek et al., 2000), lowered pain thresholds (Kinsley et al., 1988), and develop hedonic deficits (Keshet and Weinstock, 1995), while their male siblings do not. These findings are consistent with female rats being more vulnerable to PNS than are their male counterparts.

The forced swim test, developed by Porsolt (Porsolt et al., 1977), is often utilized as an assay of depressive behavior in rodents. Rats are placed in a cylindrical container filled with water and the times spent struggling, swimming, and immobile are recorded. In this test, a decrease in the duration of struggling behavior or an increase in immobility is considered indicative of depression. The validity of the Porsolt Swim Test is supported by evidence that effective anti-depressants, such as selective serotonin reuptake inhibitors, significantly reduce depressive behavior in rodents (Lucki, 1997). Conversely, amphetamine withdrawal, which is known to induce depression in humans, increases depressive behavior in the Porsolt Swim Test (Kokkinidis et al., 1986) as does PNS (Drago et al., 1999).

Gonadal hormones may influence depressive behavior of rats. Estrous cycle differences in depressive behavior on the forced swim test coincide with variations in estrogen ( $E_2$ ) levels. Proestrous rats exhibit more anti-depressant-like behavior (less immobility in the forced swim test) than diestrous or male rats (Frye and Walf, 2002). As well, administration of  $E_2$  alleviates depressive behaviors in the Porsolt Swim Test (Bernardi et al., 1989b; Galea et al., 2001; Rachman et al., 1998). Among male rats, there are circannual variations in depressive behavior. In winter months, when androgen levels are relatively lower compared to the other months, depressive behavior is increased (Abel, 1995). Further, castration increases depressive be-

havior of male rats compared to intact controls (Bernardi et al., 1989a). These findings suggest that  $E_2$  and androgens may reduce depressive behavior of female and male rats, respectively.

The purpose of these experiments was to test the hypotheses that (1) females would exhibit more depressive behaviors than males and (2) that the presence of androgens or (3)  $E_2$  would have beneficial anti-depressant effects on PNS and control rats in The Porsolt Swim Test.

## Method

These methods were pre-approved by the Institutional Animal Care and Use Committee.

### *Animals and housing*

Long-Evans rats, approximately 55 days of age, were bred in our laboratory from stock previously obtained from Taconic Farms (Germantown, NY, USA). Rats were group housed (4 per cage) in polycarbonate cages ( $45 \times 24 \times 21$  cm) until breeding and thereafter were housed individually in a temperature-controlled room ( $21 \pm 1^\circ\text{C}$ ) in the laboratory animal care facility. The rats were maintained on a 12/12 hour reversed light cycle (lights off 8:00 a.m.) with access to Purina Rat Chow and tap water in their home cages.

### *Induction of prenatal stress or control condition*

Female rats ( $n = 43$ ) were cycled through two normal estrous cycles (4–5 day cycle) and then mated. Eighteen days following mating, pregnant rats were randomly assigned to receive 45 minutes of restraint stress, under bright lights, in a plexiglas restrainer ( $n = 24$ , prenatal stress condition) or no such stress. Rats in this control condition ( $n = 19$ ) remained undisturbed in their home cages. To minimize litter effects, no more than 2 offspring from each litter were assigned to each experimental group. This type of restraint stress, on prenatal day 18, to rats disrupts the development of the hippocampus (Weinstock, 2001). Although this PNS paradigm alters hippocampal-dependent behavior and morphology, particularly of female offspring, it does not produce gross differences in the hypothalamus (Weinstock, 2001) or in sexual differentiation (Frye and Bayon, 1999; Schmitz et al., 2002).

### *Cycling of intact females*

Female offspring that remained gonadally intact ( $n = 51$ ) were screened daily between 07:00 and 08:00 h to determine those that were in behavioral estrus (Frye and Walf, 2002). Briefly, rats were placed in an arena with a male that was allowed to mount once. If the female responded to the male with a pronounced lordosis posture, the female was considered in behavioral estrus. Rats were considered in

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