Two Different Putative Genetic Animal Models of Childhood Depression

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Background: In an attempt to model childhood depression, we examined whether existing genetic animal models of depression in adult rats are also valid in prepubertal rats.

Methods: Two different “depressed” rat lines were studied: the Flinders Sensitive Line (FSL) and their controls, Sprague-Dawley (SD); and the Wistar Kyoto (WKY) line and their controls, Wistar. We hypothesized that male prepubertal FSL and WKY rats would show increased swim test immobility and different patterns of social play and of basal plasma levels of corticosterone and adrenocorticotropic hormone (ACTH) compared with control rats.

Results: Prepubertal FSL and WKY rats exhibited significantly longer duration of immobility than control rats in the swim test. The FSL rats demonstrated significantly higher levels of social play behaviors and lower levels of corticosterone and ACTH compared with SD control rats, whereas WKY rats demonstrated significantly lower levels of social play behaviors and higher plasma levels of corticosterone and ACTH compared with Wistar control rats.

Conclusions: The results might suggest that prepubertal FSL and WKY rats are both putative genetic animal models of childhood depression, exhibiting separate patterns and symptoms of childhood depression.

Key Words: Childhood depression, HPA axis, social play, animal models, swim test

Animal models of human depression have been used in attempts to understand the neurobiological basis of this disorder and to predict successful treatment strategies (Jesberger and Richardson 1985; Overstreet 1993; Pare 1989a). There are at least 18 animal models of depression, which can be divided into types, such as stress models, genetic models, pharmacological models, and miscellaneous models (Overstreet 1993, 2002). In the present research, the “depressive-like” animals were from two well-studied “genetic animal models” (Overstreet 1993, 2002; Pare 1989b, 1992, 1993, 1994, 2000; Yadid et al 2000), meeting all types of validity criteria: 1) face validity (resembles human depressive disorder); 2) construct validity (consistent with theoretical rationale); and 3) predictive validity (responds to the same drugs that affect people suffering from depression). The two lines are the Flinders Sensitive Line (FSL), initially selectively bred for hypersensitivity to cholinergic agonists from Sprague-Dawley (SD) rats, and Wistar Kyoto (WKY) rats, a line derived from Wistar rats, originally bred as normotensive controls for the spontaneous hypertensive-line rats. After these lines were established, the selection process was not continued. Adults from both lines (FSL and WKY) demonstrate depression-like symptoms (but also some symptoms that are a mismatch with depression, i.e., cognitive disturbances in the adults FSL rats [Overstreet 2002]), such as reduced body weight and disturbed rapid-eye-movement sleep. They also displayed depression-like symptoms on several behavioral tests, such as increased immobility duration in the swim test and greater degree of “anhedonia” (as measured by decreased consumption of a sweet solution) in response to chronic mild stress and acute stress. The increased immobility duration in the swim test was prevented by chronic (but not acute) antidepressant treatment (Lahman et al 1997; Overstreet 1993). Both lines have been shown to exhibit abnormalities in some central neurochemical (dopaminergic [both lines], noradrenergic [WKY], cholinergic [FSL], serotoninergic [FSL]) and peripheral hormonal (hypothalamic–pituitary–adrenal [HPA] axis [both lines], thyroid-stimulating hormone [WKY]) systems, compared with control animals (Jaio et al 2003; Overstreet 1993; Owens et al 1991; Solberg et al 2001; Yadid et al 2000). Thus, although several behavioral similarities exist between the FSL and the WKY models, they are fundamentally different. They are derived from different lines, and their patterns of neurochemical abnormalities are separate. Therefore, combined use of the two models can potentially provide convergent validity in the current study, aimed at examining the behavioral phenotype of childhood depression.

Estimates of the prevalence of child and adolescent depression are substantial, ranging from 4.8%–3% at the 0–12-year age range to 3.3%–12.4% at the 13–18-year age range (Michael and Crowley 2002; Sain-Clair 2002). Major depression in children and adolescents is common, recurrent, and associated with significant morbidity and mortality (Birmaher et al 1996a). Despite similarities in the clinical picture and longitudinal course of major depression in children, adolescents, and adults (Kovacs 1996), there are noticeable differences in the neurobiological correlates and treatment response of depressed patients in these different age cohorts (Kaufman et al 2001). Most notably, depressed children and adolescents do not show evidence of hypercortisolemia as frequently as is reported in depressed adults (Kaufman and Ryan 1999; Ryan and Dahl 1993), and depressed children and adolescents fail to respond to tricyclic antidepressants (Hazzel et al 1995). The literature on depression in children and adolescents seems to present two different categories. On the one hand, research suggests that children and adolescents differ from one another. Alterations in electroencephalographic sleep are considerably more common in depressed adolescents than in depressed children (Kaufman and Ryan 1999). Depressed...
children are reported to have a blunted growth hormone response to clonidine (Jensen and Garfinkel 1990), whereas no differences were found between depressed and control adolescents in growth hormone secretion after administration of clonidine (Jensen and Garfinkel 1990). On the other hand, other research suggests that children and adolescents are similar to each other but that both differ from adults. Thyroid hormone alterations observed in adults are not commonly reported in children or adolescents (Dorn et al 1997). Depressed adults have repeatedly been found to have elevated baseline cortisol and blunted corticotropin secretion after corticotropin-releasing hormone infusion. In contrast, depressed children and depressed adolescents failed to show such differences (Birmaher et al 1996b).

In the present study we attempted, for the first time, to determine whether “genetic animal models” are valid for modeling childhood depression. We used two behavioral tests: a modified version of the swim test of Porsolt et al (1977), and social play after 24 hours of isolation. We also weighed the animals (many depressed children exhibit weight disorders [American Psychiatric Association 2000]) and measured basal levels of the HPA hormones: corticosterone (CORT) and adrenocorticotropic hormone (ACTH). The rationale for choosing these measures, explained below, is based on some of the DSM-IV criteria for major depressive disorder and research on the psychobiology of depression. The animals were studied at the age range of 30–40 days, because at this developmental phase, before sexual maturity, rats exhibit social play, are able to show immobility in the swim test (Abel 1993), and their developing HPA system is responsive because the “stress hyporesponsive period” is behind them (Levine 2001).

Swim Test

The forced swim test, developed by Porsolt et al (1977), has become a widely used paradigm for studying stress responses and for screening antidepressant drugs (Abel 1993; but see Kawashima et al 1986). Prolonged immobility duration in this test is regarded as behavioral despair, an animal analogue of human depression. The general procedure in this paradigm is to immerse rats or mice in a cylinder of water from which there is no escape. Twenty-four hours later, rats are retested for 5 min. Typically, animals paddle vigorously when first immersed, then become relatively immobile and adopt a characteristic vertical floating response. When observed during the restet period, they are more immobile than during their initial immersion. In some variations of the test, rats are only immersed once, and immobility time is recorded during this one-time-only session (Abel and Blützke 1990; Hodgson 1991; Nishimura et al 1991). Abel (1993) has demonstrated that the vertical immobility response in the forced swim test has a sudden onset, beginning at 21 days of age and quickly stabilizing at 26 days of age. Overstreet (1993) and Yadid et al (2000) have shown longer immobility durations in adult FSL male rats compared with control rats, using the modified, one-session procedure. Similarly, Pare (1989b) has found longer immobility duration in adult WKY male rats compared with control rats. Therefore, we hypothesized that the “depressed” prepubertal rats would exhibit more immobility time in the swim test compared with their controls—exhibiting “despair” behavior, which is a well-known symptom in depressed children (American Psychiatric Association 2000).

Social Play

Social play, one of the earliest forms of non–mother-directed social behavior observed in mammals, has been observed to contain behavioral patterns related to social, sexual, and aggressive behavior, displayed in an exaggerated and/or out-of-context fashion (Vanderschuren et al 1997). One of the characteristics of social play behavior is its reward value; social play can be used as an incentive for maze-learning (Humphreys and Einon 1981; Normansell and Panksepp 1990) and place-preference conditioning (Calcagnetti and Schechter 1992; Crowder and Hutto 1992). In juvenile rats, a distinction can be made between social behaviors related to play (pinning, boxing, chasing, attacking) and unrelated to play (social exploration, contact behavior). These forms of social behavior differ regarding ontogenetic pattern. Social play behavior mainly occurs between weaning and puberty, whereas other social behaviors, not related to play, occur during the entire lifespan of rats (Vanderschuren et al 1997). Social play in most species exhibits a characteristic development time course, with the amount of play increasing during the prepubertal period (the peak in rats is approximately 35 days of age), remaining stable through youth, and diminishing as animals approach puberty (Panksepp 1998). In adult rats, the phenomenon known as social play does not exist, and only social interaction can take place. In both of the current “depressed” lines, there is no evidence in the literature for abnormal social interaction between males in “depressed” adult rats compared with their controls.

Because the play session has a rewarding value (Calcagnetti and Schechter 1992; Crowder and Hutto 1992; Humphreys and Einon 1981; Normansell and Panksepp 1990), and because depressed children tend to exhibit abnormal social interactions and play (Kovacs 1996), we hypothesized that the “depressed” lines would exhibit fewer episodes of social play compared with their controls.

HPA Hormones (CORT and ACTH)

A prominent mechanism by which the brain reacts to acute and chronic stress is activation of the HPA axis. Neurons in the paraventricular nucleus of the hypothalamus secrete corticotropin-releasing factor, which stimulates the synthesis and release of ACTH from the anterior pituitary. Adrenocorticotropic hormone then stimulates the synthesis and release of glucocorticoids (cortisol in humans, corticosterone in rodents) from the adrenal cortex. Glucocorticoids exert profound effects on general metabolism and also dramatically affect behavior through direct actions on numerous brain regions (Brown et al 1999; McEwen 2000). Of all brain systems studied in major depression, a consistent finding is that 40%–60% of drug-free depressed patients present with hypercortisolism (Gold et al 1986; Murphy 1991). Some reports suggest that chronic hypersecretion of cortisol is due to prolonged hypersecretion of corticotropin-releasing factor (Nemeroff 1984) and ACTH (Kalin et al 1982). Adrenocorticotropic hormone (but not corticosterone) levels were found to be lower in adult male FSL compared with control Flinders Resistant Line rats (Owens et al 1991). On the other hand, WKY adult rats showed higher basal levels of ACTH and corticosterone during the light phase compared with their controls (Wistar rats) (Söllberg et al 2001). Wistar Kyoto adult rats also show increased plasma ACTH levels after both chronic and acute stress relative to several other rat strains, including the Wistar rat (Pare and Rede 1993; Rede et al 1994). Because it is known that most depressed children have high levels of HPA hormones (hypercortisolism), we hypothesized that the “depressed” prepubertal lines would

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show higher levels of the HPA hormones (hypercortisolism) compared with their controls as well.

**Methods and Materials**

**Animals**

Nulliparous SD and FSL female rats were mated with male rats from the same line in their breeding colonies, in the Developmental Psychology Laboratory at Bar-Ilan University, Ramat-Gan, Israel. Both lines were likely to be inbred because of the relatively small number of original parents. Wistar Kyoto (WKY; Harlan, Jerusalem, Israel) and Wistar (Harlan, Indianapolis, Indiana) prepubertal rats were supplied by Harlan for the behavioral tests (we have since performed additional studies in our laboratory, showing that Wistar and WKY rats that were bred in our colony for several generations exhibited similar patterns of results). A second generation of WKY and Wistar rats bred in our colony provided blood samples. After weaning, male rats were housed in polypropylene cages (38 cm × 21 cm × 18 cm), three per cage, in a temperature-controlled vivarium (20°C–24°C), under a 14-hour/10-hour light/dark cycle (lights on at 5:00 AM). Food and water were available ad libitum. Separate groups of non-sibling male rats were used for each test (swim test, social play, and hormonal assays).

The study protocol was approved by the Institutional Animal Care and Use Committee and adhered to the guidelines of the Society for Neuroscience.

**Procedure**

For the swim test, after 26 to 27 hours of isolation, each male rat (aged 30–41 days) was weighed and then immersed in a Plexiglas cylinder designed especially for prepubertal rats (height 45.5 cm, diameter 14.0 cm) filled to 24 cm with fresh tap water heated to 34°C. The room in which the animals are most active, at the beginning of the night cycle (7:00–9:30 PM). Interrater reliability on the floating measure was .948, p < .001 (n = 12 in each group).

Play testing was conducted in a clear Plexiglas chamber (38 cm × 21 cm × 18 cm), the floor of which was covered with approximately 1 cm of pine shavings. The room in which the chamber was located was darkened during testing, and the chamber was illuminated by a single 25-W red light bulb, place approximately 50 cm above the base of the chamber. Sessions were filmed with a Sony High-8 video camera (Tokyo, Japan) placed 130 cm above the cage.

After 24 hours of isolation (a standard procedure that enhances the likelihood of rapidly observing play [Calcagnotto and Schechter 1992]), each male rat (aged 34 to 35 days and without swim-test experience) was filmed for 15 min in a cage with an unfamiliar rat from the same line but not from the same litter. All tests were performed between 9:00 and 11:00 AM. Frequencies of behaviors were analyzed from the videotapes, within line pairs. Behaviors examined were boxing, chasing, pinning, attacking, contact behavior, and social exploration (Kalin et al 1982; Meaney and Stewart 1981). Interrater reliabilities on scoring these behaviors ranged from r = 1.1 to r > .941, (p < .001) (n = 14 in each group).

For hormonal assays, after decapitation (rats were waiting outside of the decapitation room), trunk blood was collected into chilled tubes containing ethylenediaminetetraacetic acid solution. Blood samples were collected carefully; after each animal (males only), gloves were changed and all the equipment was cleaned to prevent pre-decapitation stress. Samples were centrifuged for 10 min at 4°C at 2500 rpm, and plasma was stored at −80°C until determination. On the day of assay, frozen plasma samples were thawed, and plasma ACTH and CORT levels were measured with commercial radioimmunoassay (RIA) kits (rat CORT RIA kit: Diagnostic Products Corporation, Los Angeles, California; ACTH RIA kit: Immuno Biological Laboratories, Hamburg, Germany). Each group was composed of 10–15 animals.

**Data Analysis**

Group differences in weight and floating time were analyzed by one-way analysis of variance (ANOVA) comparing each “depressed” and control line separately (FSL and SD; Wistar and WKY). The social behavior of the groups was compared by one-way multivariate analysis of variance (MANOVA), followed by one-way univariate ANOVA for each of the six measures of social play and behavior, for each of the two comparisons. Basal levels of ACTH and CORT were analyzed by t tests for independent samples, comparing the FSL and SD lines and the WKY and Wistar lines separately.

**Results**

The immobility data are presented in Figures 1 and 2. As evident from the figures, both FSL and WKY lines exhibited significantly longer immobility duration in the swim test compared with their control lines [SD–FSL: F(1,22) = 25.77, p < .05; Wistar–WKY: F(1,28) = 59.45, p < .01]. The FSL rats weighed significantly less (mean ± SEM = 101.1 ± 3.48 g) than SD rats (129.3 ± 4.34 g) [F(1,22) = 25.77, p < .01], and WKY rats weighed significantly less (131.6 ± 2.65 g) than Wistar control rats (157.9 ± 2.14 g) [F(1,28) = 31.14, p < .01].

To determine whether the weight of the animals could have influenced the immobility duration (because both of the control lines weighed more than the “depressed” lines and they also showed less immobility duration in the swim test), we compared the weight and immobility duration between the control lines (Wistar and SD). One-way ANOVA revealed that the Wistar prepubertal rats weighed 157.9 ± 3.03 g, significantly more than the SD rats (129.3 ± 3.39 g) [F(1,25) = 39.47, p < .001]. Nevertheless, the SD prepubertal rats exhibited significantly less immobility duration (54.5 ± 11.94 sec) in the swim test com-

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**Figure 1.** Immobility duration in sec (mean ± SEM) of 30- to 31-day-old Sprague-Dawley (SD) and Flinders Sensitive Line (FSL) rats (n = 12 in each group). *p < .05.

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pared with the Wistar rats (162.8 ± 10.686 sec) \(F(1,25) = 45.653, p < .001\). This suggests the absence of a significant influence of body weight on immobility duration in the swim test.

Regarding social behaviors, MANOVA revealed, surprisingly, that prepubertal FSL rats demonstrated, overall, significantly higher levels of social play behaviors compared with their SD controls \(F(6,21) = 13.94, p < .01\) (Figure 3). One-way ANOVA revealed that FSL rats demonstrated higher levels of social play on all measures [boxing: \(F(1,26) = 5.14, p < .05\); pinning: \(F(1,26) = 4.75, p < .05\); attacking: \(F(1,26) = 5.40, p < .05\); chasing: \(F(1,26) = 67.80, p < .01\) and lower levels of contact behavior \(F(1,26) = 5.06, p < .05\), which is a social behavior that is not related to play (Kaslow and Wamboldt 1985). In contrast, MANOVA revealed that the WKY rats demonstrated, overall, significantly lower levels of social play behaviors compared with Wistar control rats (Figure 4). One-way ANOVA revealed that WKY rats demonstrated lower levels of social play on all measures [boxing: \(F(1,26) = 5.74, p < .05\); pinning: \(F(1,26) = 7.33, p < .05\); chasing: \(F(1,26) = 25.45, p < .01\); attacking: \(F(1,26) = 7.93, p < .01\)]. Wistar Kyoto rats also demonstrated significantly lower levels of contact behavior \(F(1,26) = 24.79, p < .01\) and social exploration \(F(1,26) = 8.85, p < .05\), which are social behaviors that are not related to play.

\(T\)-tests for independent samples revealed significant differences between prepubertal FSL and SD and between WKY and Wistar rats in the basal plasma levels of CORT and ACTH. The FSL rats exhibited lower levels of CORT \(t(12) = 3.65, p < .01\) and ACTH \(t(14) = 2.99, p < .01\) compared with their SD controls (Figures 5 and 6), whereas WKY exhibited higher levels of CORT \(t(19) = 3.97, p < .01\) and ACTH \(t(12) = 2.79, p < .05\) compared with the Wistar rats (Figures 5 and 6).

### Discussion

Childhood depression has received attention as a significant clinical phenomenon only relatively recently, and was almost completely ignored until the 1970s. The dramatic change in interest taken by child psychiatrists in affective disorders has arisen from two major areas of advance in adult psychiatry: diagnostic theory and the advances in the biochemical, genetic, and therapeutic understanding of affective disorders in adults (Apter and Tyano 1984). These changes facilitated recognition that symptoms found in adults with major depression can be found in children. Indeed, studies from the 1980s supported the diagnostic validity of using the adult DSM-III (American Psychiatric Association 1980) criteria for major depressive disorder, dysthymic disorder, and adjustment disorder with depressed mood in a school-aged cohort (Kaslow and Wamboldt 1985). Although there are some similarities in research findings observed across the life cycle, children and adolescents have been found to differ from depressed adults on measures of basal cortisol secretion, corticotropin stimulation after corticotropin-releasing hormone infusion, response to several serotonergic probes, immunity indices, and efficacy of tricyclic medications (Kaufman et al 2001). These differences are proposed to be related to developmental factors, stage of illness, and heterogeneity in clinical outcome.

The purpose of this study was to examine whether two different adult animal models for depression are also valid for
modelling childhood depression. First, we compared the weights of the “depressed” prepubertal lines and their controls and found that the “depressed” lines weighed less than their controls. Similarly, depressed children often have weight disorders (American Psychiatric Association 2000). In the most widely used paradigm for studying stress responses and screening antidepressant drugs (Abel 1993), the swim test, both FSL and WKY prepubertal rats exhibited significantly longer immobility durations than their respective control lines, suggesting “behavioral despair.” When we compared the weight and the immobility duration of the control lines, we further found that although the Wistar prepubertal rats weighed more than the SD rats, they exhibited a longer immobility duration in the swim test, suggesting that weight has no direct influence on the immobility duration in the swim test and that the differences found between the “depressed” lines and their controls cannot be attributed to weight differences.

In the social play test, assessing the most prominent behavior evident in the period between weaning and puberty, the results suggest that the two lines exhibit separate patterns of abnormal social behavior: whereas the FSL rats demonstrated much higher levels of social play behaviors compared with their controls and lower levels of social behavior that is not related to play, WKY rats demonstrated much lower levels of social play and even lower levels of social behavior that is not related to play. The absence of normal play, together with antisocial behavior, avoidance, and withdrawal is one of the clinical symptoms of childhood depression (American Psychiatric Association 2000; Kaslow and Wamboldt 1985; Kazdin 1990).

When we examined the system that manages the body’s response to stress, the HPA axis, both lines exhibited altered patterns of basal plasma levels of hormones: compared with their controls, prepubertal WKY rats showed increased levels of CORT and ACTH, a phenomenon called hypercortisolism. In contrast, prepubertal FSL rats showed lower levels of CORT and ACTH compared with their controls, a phenomenon called hypocortisolism. This latter phenomenon might, in fact, persist, at least partially, into adulthood: ACTH (but not CORT) levels were found to be lower in adult male FSL rats compared with control Flinders Resistant Line rats (Owens et al 1991). We note also that recent studies in our laboratory of acute and chronic stress effects on the HPA axis further replicate and support the difference between the lines in basal levels and extend the differences to stress reactivity (Malkesman et al, unpublished data). Nevertheless, additional replication studies by other laboratories would further strengthen the confidence in these findings.

Hypercortisolism, as revealed in our WKY line, is one of the most robust phenomena in biological psychiatry associated with major depression (Gold et al 1988). Ever since the seminal studies by Selye (1956), stress has been associated with activation of the HPA axis, resulting in increased secretion of cortisol from the adrenal glands. In recent years, however, a novel and paradoxical phenomenon has emerged from neurobiological studies of the effect of stress—hypocortisolism (Heim et al 2000). There is increasing evidence for a relatively decreased (rather than increased) cortisol secretion in individuals who have been exposed to severe stress or suffer from stress-related disorders, and it has been reported recently in several studies that hypocortisolism can be found among children growing up under less than optimal conditions of care (Gunnar and Vazquez 2001). There are also studies revealing lower morning cortisol levels for maltreated, depressed children (Hard et al 1996; Kaufman 1991). Although trauma and neglect characterize the situations associated with low cortisol, there have also been several studies of antisocial children and their families that have demonstrated lower than expected cortisol levels (Gunnar and Vazquez 2001). A few studies (McBurnett et al 1991, 2000; Vanyukov et al 1993) reported that boys referred for disruptive, aggressive behavior have remarkably low cortisol concentrations. Furthermore, depressive symptoms in childhood have been shown to predict psychiatric symptoms (mainly aggression) in young adulthood (Aronen and Soininen 2000). Exposure to violence, chaotic families, and poor parent–child relationships are experiences in the lives of antisocial, aggressive children. Thus, the association of antisocial behavior with low cortisol described for these children might reflect the chronic stress of their lives. In accordance, the FSL pups in our current study, growing up under less than optimal care (with “depressed” mothers [Lavi-Avnon et al 2005a, 2005b] and siblings) displayed lower basal plasma levels of CORT and ACTH—hypocortisolism. We therefore interpret the abnormally high levels of social play (e.g., chasing, boxing, attacking) found in the prepubertal FSL rats as (which might seem to be in conflict with the view of FSL rats as a model of depression) reflecting aggressive and antisocial behavior, which are phenomena that can be found in depressed children (Messer and Gross 1994; Patterson et al 1997). This hypothesis should be supported by future experiments showing that these prepubertal animals turn into aggressive adults.

Viewing the two lines used in these studies as models of childhood depression relies on the strength of the converging evidence from several measures, because depression is a multi-symptom syndrome. Therefore, further studies of additional measures that assess other aspects of depressive-like behavior in rats could provide additional evidence. The well-known common comorbidity between anxiety and depression further suggests studies of anxiety-like behaviors in these models, a task we are currently undertaking. We also note that the two sets of rats used for behavioral studies were bred in different facilities, and this different early experience could have affected the results.

In sum, the results might suggest that prepubertal FSL and WKY lines are both genetic animal models of childhood depression, exhibiting separate patterns of social dysfunction and opposite patterns of HPA axis modulation. In general, however, the data on the WKY rats would seem most consistent with a depressive profile. The FSL profile might possibly be related to chronic stress, and its role as a potential model of childhood depression requires further support. These two different putative genetic animal models of childhood depression can help in the attempts to understand the neurobiological basis and to predict...
successful treatment strategies for different patterns of this pathology (Nestler et al 2002; Vanderschuren et al 1995).

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