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# The Flinders Sensitive Line Rat Model of Depression—25 Years and Still Producing

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**Abstract**—Approximately 25 years have passed since the first publication suggesting the Flinders sensitive line (FSL) rat as an animal model of depression. At least 6 years of research on these rats was completed before that seminal paper, and there has been a steady stream of publications (130+) over the years. The present review will focus on several issues not previously covered in earlier reviews, summarize the several lines of ongoing investigations, and propose a novel mechanism that accounts for a number of previously unexplained observations. A key observation in the FSL rat relates to the antidepressant (AD)-like effects of known and putative antidepressants. The FSL rat typically exhibits an AD-like effect in

behavioral tests for AD-like activity following chronic (14 days) treatment, although some studies have found AD-like effects after fewer days of treatment. In other observations, exaggerated swim test immobility in the FSL rat has been found to have a maternal influence, as shown by cross-fostering studies and observations of maternal behavior; the implications of this finding are still to be determined. Ongoing or recently completed studies have been performed in the laboratories of Marko Diksic of Canada, Aleksander Mathé of Sweden, Gregers Wegener of Denmark, Brian Harvey of South Africa, Paul Pilowsky and Rod Irvine of Australia, and Gal Yadid of Israel. Jennifer Loftis of Portland, Oregon, and Lynette Daws of San Antonio,

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Texas, have been working with the FSL rats in the United States. A puzzling feature of the FSL rat is its sensitivity to multiple chemicals, and its greater sensitivity to a variety of drugs with different mechanisms of action. It has been recently shown that

each of these drugs feeds through G protein-coupled receptors to potassium-gated channels. Thus, an abnormality in the potassium channel could underlie the depressed-like behavior of the FSL rats.

## I. Introduction

The Flinders sensitive line (FSL) rat has been purported to be a genetic animal model of depression because of several features that resemble human depressives, including elevated rapid eye movement (REM) sleep and an exaggerated swim test immobility that can be reduced by chronic antidepressant treatments. Previous reviews (Overstreet, 1993, 2002; Overstreet et al., 2005) have provided further details. On the 25th anniversary of the first publication examining the FSL model (Overstreet, 1986), the present review aims to 1) discuss several critical issues that have not been given adequate attention in past reviews, and 2) survey the recent literature from colonies of FSL rats that now exist worldwide (Australia, Canada, Denmark, Greece, Israel, South Africa, Sweden, United States). Of more than 130 articles reporting on FSL rats, 12 were published in 2011.

## II. Pre-model Findings

It must be emphasized that we had no intention of creating an animal model of depression. The original intent of our work was to create a strain of rat that was resistant to the anticholinesterase agent, diisopropyl fluorophosphate (DFP). The mechanisms underlying this resistance were to be compared with those previously established for rats that became tolerant to DFP following chronic treatment (Russell et al., 1982; Russell and Overstreet, 1987). However, the selective breeding program did not result in a resistant strain of rat; instead, a strain of rat that became progressively more sensitive to DFP was established, with the other strain, sometimes called the Flinders resistant line (FRL), resembling control Sprague-Dawley (SD) rats (Overstreet et al., 1979b).

Because of extensive knowledge of the mechanisms underlying tolerance to DFP (Russell and Overstreet, 1987), we were able to devise experiments that investigated the mechanisms underlying the increased sensitivity of the FSL rats. In contrast to tolerant animals, FSL rats were more sensitive to cholinergic agonists (Overstreet and Russell, 1982; Overstreet et al., 1984) and had elevated muscarinic receptors (Overstreet et al., 1984; Daws and Overstreet, 1999). However, like tolerant rats, the FSL rats did not show

any changes in the enzyme acetylcholinesterase (Sihotang and Overstreet, 1983; Overstreet et al., 1984). Thus, the primary basis of the increased sensitivity of the FSL rat was an increase in muscarinic receptors. This pre-project work also established that female rats were less sensitive than their male counterparts to the effects of DFP (Overstreet et al., 1979a, 1984; Russell et al., 1983), but both male and female FSL rats were more sensitive to cholinergic agonists than the FRL or "normal" SD rats (Overstreet et al., 1979a, 1984; Russell et al., 1983).

## III. The Initial Model

The cholinergic supersensitivity of the FSL rats served as a major factor in their initial development. During a meeting with David Janowsky in 1984, the features of the FSL rat were being described. Dr. Janowsky jumped up, said the rats were just like depressed humans, and retrieved several reprints out of his filing cabinet. Indeed, there was a great similarity between depressed humans (Janowsky et al., 1980; Overstreet et al., 1988) and the FSL rat (Overstreet and Russell, 1982; Overstreet et al., 1988). Consequently, Overstreet spent most of his sabbatical from 1985 to 1986 at the University of California at San Diego, studying the FSL rats instead of depressed humans as originally planned. The FSL rats exhibited increased REM sleep, a cholinergically mediated process, as do depressed individuals (Shiromani et al., 1988; Benca et al., 1996). Moreover, both FSL rats and depressed humans show a greater hormonal response to a cholinergic agonist challenge (Overstreet et al., 1986; Risch et al., 1991). Thus, these studies further strengthened the degree of similarity between the FSL rats and depressed individuals. Therefore, in the initial model, the exaggerated swim test immobility of the FSL rat was just one component of a cholinergic supersensitivity model.

### Validity of FSL Model, Including Comparison with Other Animal Models of Depression

The validity of an animal model is usually based upon three criteria: face validity, construct validity, and predictive validity. The reader is referred to earlier

**ABBREVIATIONS:** 5-HT, 5-hydroxytryptamine (serotonin); AD, antidepressant; BDNF, brain-derived neurotrophic factor; DFP, diisopropyl fluorophosphate; ECS, electroconvulsive stimuli; FH, fawn-hooded; FRL, Flinders resistant line; FSL, Flinders sensitive line; GIRK, G protein-coupled, inward rectifying potassium; NO, nitric oxide; NPS, neuropeptide S; NPY, neuropeptide Y; REM, rapid eye movement; SD, Sprague Dawley; SwHi, swim high-active; SwLo, swim low-active; WKY, Wistar Kyoto.

reviews of the FSL rat (Overstreet, 1993, 2002; Overstreet et al., 2005) for additional details. A listing of other selectively bred animal models of depression is given in Table 1. The FSL rat resembles depressed individuals in several respects, so it can be regarded to have a modest degree of face validity. The FSL rat has elevated REM sleep compared with the control FRL rats (Shiromani et al., 1988; Benca et al., 1996). This observation has also been made in depressed individuals (see Benca et al., 1996). Another similarity is the increased passive or inhibitory behavior following stress. The most common example of this behavior in the FSL rat is its exaggerated immobility in the swim tank. Therefore, FSL rats exhibits some similarities to depressed humans.

Despite these similarities, the FSL rats do not share all the behaviors of depressed humans. A key symptom of depression, anhedonia, is not seen in this strain. Initially, testing for the preference of sweet solutions failed to detect any differences between the FSL and FRL rats (Pucilowski et al., 1993). However, when the two strains were subjected to chronic mild stress, a procedure that produces a reduction in sweet intake (or anhedonia) (Willner, 2005), the FSL rat showed a greater reduction in sweet intake (Pucilowski et al., 1993). However, the FSL and FRL rats bar-pressed at similar rates for rewarding brain electrical stimulation (Matthews et al., 1996), confirming that there are no differences in anhedonia under nonstressed conditions. Thus, the FSL rat resembles depressed individuals in some respects but not all, perhaps not surprising given the heterogeneous nature of depressive disorders.

Several hypotheses have been proposed regarding neurochemical systems that might be impaired in depressed individuals. The FSL rat would be regarded as demonstrating construct validity if it exhibits neurochemical abnormalities that are similar to those found in humans. Abnormal serotonergic system function is one of the most enduring theories regarding depression, and there is much data for serotonergic abnormalities in FSL rats. Early on, Zangen et al. (1997) reported that elevated tissue levels of serotonin [5-hydroxytryptamine (5-HT)] in FSL rats were normalized by treatment with antidepressants. In more

recent parallel experiments, Hasegawa et al. (2006) demonstrated that both FSL rats and depressed individuals exhibited reduced serotonin synthesis. Another system that seems to be altered in both FSL rats and depressed humans is the cholinergic system. Increased sensitivity to cholinergic agonists has been observed in both FSL rats (Overstreet et al., 1998a) and depressed humans (Janowsky et al., 1994). Finally, neuropeptide Y (NPY) has been reported to be decreased in both depressed humans (Wu et al., 2011) and FSL rats (Caberlotto et al., 1999; Jimenez-Vasquez et al., 2000). Consequently, we conclude that the FSL rat satisfies the criterion of construct validity.

Predictive validity refers to the ability of the animal model to detect antidepressant-like activity of drugs that are either known antidepressants or were found to be antidepressants upon later testing. A tremendous number of drugs have been used in the FSL rats, and these findings are summarized in the next section and in Table 2. Only a few key points will be elaborated here. All drugs that have antidepressant effects in humans have been found to show an antidepressant-like effect in the FSL rat, evidenced by a reduction in swim test immobility (see next section). For example, early work showed that melatonin agonists but not antagonists had antidepressant-like effects in the FSL rat (Overstreet et al., 1998b), and later studies showed that agomelatine, which is an agonist at melatonin receptors, had antidepressant effects in humans (Green, 2011; Sansone and Sansone, 2011). Finally, the psychostimulants amphetamine and scopolamine, which have antidepressant-like effects when tested within 1 hour of treatment, do not have antidepressant-like effects when tested 24 hours after a chronic regimen (Overstreet et al., 1995). Therefore, the predictive validity of the FSL rat is quite high.

There are various other selectively bred animal models of depression (see Table 1 for a brief overview). In fact, there are so many models that it is not possible to do justice to them all; the reader may consult Overstreet (2012) and Wegener et al. (2012) for further details. The Wistar Kyoto (WKY) rat is a control rat bred in parallel to the spontaneously hypertensive rat, but Pare (1989, 1992) noted a number of behavioral

TABLE 1

Overview of selectively bred animal models of depression		
Selectively Bred Depression Model	Strain	Main References
WKY	Rats	Lahmame et al., 1997; Pare and Redei, 1993; Will et al., 2003
FSL/FRL	Rats	Overstreet, 1986; Overstreet et al., 2005
SwLo/SwHi	Rats	West and Weiss, 1998
LR/HR	Mice	Touma et al., 2008
cLH/cNLH	Rats	Vollmayr et al., 2001; Vollmayr and Henn, 2001
Fawn-hooded (FH/Wjd)	Rats	Rezvani et al., 2007

cLH, inbred learned helpless; cNLH, inbred not learned helpless; FRL, Flinders resistant line; FSL, Flinders sensitive line; HR, high reaction to stress test; LR, low reaction to stress test; SwHi, swim high-active; SwLo, swim low-active; WKY, Wistar Kyoto.

TABLE 2

Drugs that have elicited an AD-like effect in the FSL rat after chronic treatment

Drug (mg/kg)	Dose	Drug Class	Change in Swimming	References
Desipramine	5	Tricyclic	Significant increase	Pucilowski and Overstreet, 1993
Desipramine	5	Tricyclic	Significant increase	Schiller et al., 1992
Desipramine	5	Tricyclic	Significant increase	Zangen et al., 2001
Sertraline	5.7	SSRI	Significant increase	Pucilowski and Overstreet, 1993
Imipramine	15	Tricyclic	Significant increase	Schiller et al., 1992
DFP	1	Anticholinesterase	No Change	Schiller et al., 1992
SSR125543	3, 30	CRF1 antagonist	Significant increase	Overstreet and Griebel, 2004 <sup>a</sup>
SSR58611A	1, 3	$\beta$ 2 NA agonist	Significant increase	Overstreet et al., 2008 <sup>a</sup>
Nemifitide	0.3	Analog of MIF	Significant increase	Overstreet et al., 2004a <sup>a</sup>
Amphetamine	2	Stimulant	No change	Overstreet et al., 1995
Scopolamine	2	Anticholinergic agent	No change	Overstreet et al., 1995
SSR149415	10, 30	V1b antagonist	Significant increase	Overstreet and Griebel, 2005
CP154,526	10 $\times$ 2	CRF1 antagonist	Significant increase	Overstreet et al., 2004b <sup>a</sup>
Citalopram	5, 10	SSRI	Significant increase	Overstreet et al., 2004b <sup>a</sup>
Saredutant	1, 10	NK2 antagonist	Significant increase	Overstreet et al., 2010a <sup>a</sup>
Paroxetine	7.5	SSRI significant	Increase	Mork et al., 2011
Paroxetine	7.5	SSRI	Significant increase	Zangen et al., 2001
Ondansetron	1, 10	5-HT <sub>3</sub> antagonist	Significant increase	Mork et al., 2011
Lu AA33810	3, 10	NPY Y5 antagonist	Significant increase	Walker et al., 2009
S 20304	1, 20	Melatonin agonist	Significant increase	Overstreet et al., 1998a
S 20928	1, 10	Melatonin antagonist	No change	Overstreet et al., 1998a
Inositol	1200	Precursor to inositol	Significant increase	Einat et al., 2002
Nicotine	0.4	Nicotine agonist	Significant increase	Tizabi et al., 1999
NGF	Many	Trophic factor	Significant increase	Overstreet et al., 2010b

CRF1, corticotropin-releasing factor 1; MIF, melanocyte inhibiting factor; NGF, nerve growth factor; NK2, neurokinin 2; SSRI, selective serotonin reuptake inhibitor; V1b, vasopressin V1b receptor; SSR125543, 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine; SSR58611A, amibegron (ethyl [(7S)-7-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydronaphthalen-2-yl]oxy)acetate); SSR149415, nelivaptan ((2S,4R)-1-[(3R)-5-chloro-1-(2,4-dimethoxyphenyl)sulfonyl-3-(2-methoxyphenyl)-2-oxo-indolin-3-yl]-4-hydroxy-N,N-dimethyl-pyrrolidine-2-carboxamide); CP154526, N-butyl-N-ethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)pyrrolo[3,2-e]pyrimidin-4-amine; Lu AA33810, N-[(trans-4-[(4,5-dihydro[1]benzothiepinol[5,4-d]thiazol-2-yl)amino]cyclohexyl)methyl]methanesulfonamide; S 20304, N-(2/7-methoxy-1-naphthyl)ethyl)cyclopropanecarboximide; S 20928, N-(2-(1-naphthyl)ethyl)cyclobutanecarboximide.

<sup>a</sup> These studies included a tricyclic and/or an SSRI as a positive control, and the study drugs significantly increased swim test behavior (reduced immobility).

abnormalities. Further work, including some comparisons with the FSL rat, has shown that the WKY rat exhibits both anxiogenic and depressogenic behavior (Malkesman et al., 2009) and elevated REM sleep (Dugovic et al., 2000). Thus, unlike the FSL rat, the anxiety-like behavior of the WKY rats is more widespread. The WKY rat responds with a variable degree to antidepressants (Lahmame et al., 1997; Lahmame and Armario, 1996; Lopez-Rubalcava and Lucki, 2000) and has therefore been proposed as a model of treatment-resistant depression (Lahmame et al., 1997). The model has been further developed into “WKY most immobile” and “WKY least immobile” rats (Will et al., 2003).

The fawn-hooded (FH) rat was derived from the selective breeding program for hypertension. This rat exhibits increased immobility in the swim test that is reduced by certain antidepressants (Overstreet et al., 2007; Rezvani et al., 2007). However, this rat also drinks copious amounts of alcohol voluntarily, and studies of this field have left little time to focus on the depressed-like behavior. It has been found, nevertheless, that antidepressants given to FH rats that have access to alcohol do not affect alcohol intake (Overstreet et al., 2007). A similar finding has been reported in humans (Pettinati, 2004). The FH rats exhibit abnormalities in central serotonergic function (Arora et al., 1983; Aulakh et al., 1994; Bendotti and Samanin, 1987; Dumbrille-Ross and Tang, 1981), but whether these serotonergic

abnormalities contribute to their behavior remains to be determined. Interestingly, the first results showing decreased NPY expression in hippocampal fibers in a model of depression were obtained in FH rats; these changes were reversed following electroconvulsive stimuli (ECS) (Mathé et al., 1998). These findings were of great heuristic value as they led to subsequent identification of reduced NPY expression in both genetically and environmentally based rodent models of depression, including the previously described FSL rat model.

Because low motor activity and passive stress coping in a swim test have been proposed to represent depression-like behavior in the rat, SD rats have been bred in accordance with their motor activities since 1987 (Weiss et al., 1998). Two rat lines have been obtained, swim low-active (SwLo) and swim high-active (SwHi), which differ dramatically in forced swim test (FST) behavior. The SwLo rats show little struggling and much floating, whereas SwHi rats show the reverse (Weiss et al., 1998). Importantly, when SwLo rats were given an antidepressant, chronic but not acute administration increased their swim test activity (West and Weiss, 1998a). Information on neurotransmitter involvement was limited, but studies suggest involvement of both glutamatergic (Tabb et al., 2007) and dopaminergic (West et al., 1999a; West et al., 1999b) mechanisms as well as alterations of the stress axis (Gutman et al., 2008).

Since dysfunctions (hyper- or hypoactivity) of the hypothalamic-pituitary-adrenal axis may play a prominent role in the development of major depressive disorders (Bale, 2006; De Kloet et al., 1998; Holsboer, 2000), researchers have attempted to generate animal models that mimic these neuroendocrine core symptoms with the goal of unraveling the parameters underlying increased or decreased stress reactivity (Touma et al., 2008). Mice expressing hyper- or hypo-reactivity of the hypothalamic-pituitary-adrenal axis were selected for the “high reactivity” and “low reactivity” breeding line. Compared with the low-reactivity animals, the high-reactivity males and females were “hyperactive” in some behavioral paradigms (Touma et al., 2008), resembling the symptoms of restlessness and agitation often seen in melancholic depression. On the neuroendocrine level, the circadian rhythm of glucocorticoid secretion revealed a flattened diurnal rhythm (Touma et al., 2008), mimicking findings from patients suffering from melancholic depression (Deuschle et al., 1997; Keller et al., 2006).

There are also a variety of environmental methods to induce depressed-like behavior in rats. Chronic mild stress employs a variety of mild stresses in a random fashion to induce anhedonia, as measured by sweet intake and preference (Willner, 2005). Appropriate treatment with antidepressants prevents the decrease in sweet intake (Willner, 2005). Another model is learned helplessness, where a rat is subjected to an inescapable shock and is later observed to fail to avoid shock (Henn and Vollmayr, 2005; Pryce et al., 2011). However, in outbred rats, the entire proportion of shock-trained animals does not become helpless. Therefore, breeding of helpless lines from Harlan SD outbred rats was initiated in 1990 to achieve a higher yield of helpless animals following inescapable shock-training (Henn and Vollmayr, 2005; Vollmayr and Henn, 2001). This resulted in congenitally learned helpless rats that exhibit a helpless phenotype without exposure to uncontrollable shock, and a congenitally not learned helpless strain that is resistant to the effects of inescapable shock (Vollmayr and Henn, 2001).

Finally, some investigators separate pups from their mother prior to weaning and characterize the depressed-like behavior when adults (Millstein and Holmes, 2007). This paradigm has been adopted by the Swedish group in their recent studies. By combining maternal separation with the genetic variable (FSL versus FRL), a more complete picture is obtained.

#### IV. Antidepressant-Like Effects

The forced swim test that is commonly used to observe FSL rat behavior has several key elements, including:

1. There is only a single 5-minute exposure to the water tank. The standard Porsolt procedure of a 15-minute pretest and a 5-minute test swim was not used because the FSL rat is highly immobile without pre-exposure (Overstreet et al., 2005; Schiller et al., 1992; Pucilowski and Overstreet, 1993).
2. The rats are chronically treated with antidepressants, usually for 14 days. So far, only one drug has shown an AD-like effect after acute treatment (Majumder et al., 2011), but it is not clear whether the effect is truly antidepressant or simply a consequence of the activating effects of 3,4-methylenedioxymethamphetamine (MDMA). Several drugs have produced an AD-like effect after just 5 days of treatment. These include desipramine, a tricyclic antidepressant; nemifitide, an analog of melanocyte inhibitory factor; and a corticotropin-releasing factor 1 receptor antagonist (Overstreet and Griebel, 2004; Overstreet et al., 2004a,b, 2008).
3. The rats are tested about 24 hours after the last treatment, when no acute effects of the drug would be expected. One consequence of this procedure is that we have been able to eliminate amphetamine and anticholinergic agents as potential antidepressants. In the standard Porsolt test, these psychostimulants are false positives because the swim test is given 60 minutes after the last drug treatment, and the activating effects of the drugs lead to an increase in swimming. When the test is performed 24 hours after the last drug treatment, there is no stimulant effect (Overstreet et al., 1995).

A very large number of drugs with very different mechanisms of action have been tested against the exaggerated swim test immobility in the FSL rats. Table 2 includes the drug, dose, suspected drug class, and change in swim test score. The studies on drugs having AD-like effects are often supported by other studies, suggesting an AD-like effect (e.g., amibegron, a  $\beta$ 3-adrenoceptor agonist) or represent the first extensive report (e.g., nerve growth factor). Equally important is that chronic treatment of the FRL or control rats with antidepressants or putative antidepressants has consistently failed to have AD-like effects (Overstreet and Griebel, 2004, 2005; Overstreet et al., 2004a). The drugs only “work” in rats with exaggerated immobility.

One of the standard conditions may be modified to obtain more information about the AD-like effects of the drugs. For example, it has been determined that several drugs with AD-like effects lose those effects if the dose is reduced by 50% (Overstreet et al., 2004b). This fact allows for studies of synergism in which two drugs at ineffective doses may be combined to produce an AD-like effect. Saredutant, neurokinin-2 receptor antagonist, has a synergistic effect with desipramine (Overstreet

et al., 2010), whereas ondansetron, a 5-HT<sub>3</sub> antagonist, is synergistic with paroxetine (Mork et al., 2011).

Another variable that has been manipulated is time. It was found, for example, that desipramine and nemifitide had antidepressant-like effects within 5 days but fluoxetine did not (Overstreet et al., 2004b). In contrast, when the time was lengthened between the last treatment of a 14-day regimen and the behavior test to 5 days, fluoxetine and nemifitide still had AD-like effects but desipramine did not (Overstreet et al., 2004b). These findings are similar to those that formed the foundation for the nemifitide dosing schedules used in humans (Feighner et al., 2003).

Thus, a tremendous amount of data has been collected on the putative AD-like effects of drugs in the FSL rat using the forced swim test. So far, the FSL rat has shown an AD-like effect for all compounds that were predicted to have these effects. Furthermore, it has failed to detect AD-like effects for drugs that would not be expected to have AD-like effects, including those that gave false-positive effects in the Porsolt test. For novel ADs, the ultimate test will come from clinical trials of the drugs for which currently there is scant information. Of note, however, a compound with a melatonin agonist action has shown some promise in clinical studies (Green, 2011; Sansone and Sansone, 2011). Some investigators have reported an AD-like effect of scopolamine in humans (Furey and Drevets, 2006; Drevets and Furey, 2010; Furey et al., 2010), although other articles have reported negative effects (Howland, 2009). In addition, the positive studies used an atypical treatment design, with scopolamine being given intravenously over 3 consecutive days (Furey and Drevets, 2006; Drevets and Furey, 2010; Furey et al., 2010). It remains to be determined whether there is a mismatch for the findings on scopolamine in the FSL rat versus those from the clinical setting.

## V. Social Interaction Test

Anxiety is not considered a core feature of depression, but there exists a high degree of comorbidity of anxiety with depression. Therefore, the behavior of FSL rats was examined in the classic test of anxiety-like behavior, the elevated plus maze, which is an unconditioned test for anxiety in rodents that works by creating a conflict between an animal's exploratory drive and its fear of open and brightly lit areas. Under baseline conditions, no differences were discovered between the FSL and FRL lines (Overstreet et al., 1995). Treatment with a benzodiazepine exerted a similar anxiolytic effect in both FSL and FRL rats and did not differentiate between the two strains (Schiller et al., 1991). Therefore, it had been claimed for many years (e.g., Overstreet, 1993) that the FSL rat was a "pure" animal model of depression.

However, recent results demonstrated that FSL rats had a reduced level of anxiety on the elevated plus maze compared with the FRL rats (Abildgaard et al., 2011). Specifically, the FSL rats spent more time on the open arms and had a higher level of full entries into open arms. Similar findings have been described in young FSL rats compared with SD rats (Braw et al., 2006). On the other hand, it is interesting to note that FSL rats did exhibit anxiogenic behavior in the social interaction task (Overstreet et al., 2004a), which may reflect enhanced social anxiety or, alternatively, reduced social motivation and social withdrawal. Almost all reports on this task suggest that it is measuring anxiety-like behavior (File and Seth, 2003), but is it possible that it is measuring a depressed-like behavior in the FSL rat? Social withdrawal is certainly a key behavioral symptom of depressed individuals.

Taken together, as anxiety does not seem to be a prominent feature of the FSL strain, the FSL rats seem to be a model for depression without comorbidity of anxiety. However, as anxiety can be judged from multiple paradigms, further studies are warranted.

## VI. Maternal Effects

Studies of maternal behavior of the FSL rats and their controls revealed a number of deficiencies in the FSL rats. They spent less time nurturing their young (Lavi Avnon et al., 2005). It is not surprising, therefore, that their swim test immobility was altered by cross-fostering. FSL pups that were cross-fostered to FRL dams were less immobile in the forced swim test, but cross-fostered FRL rats were unaffected (Friedman et al., 2006). In effect, the abnormal maternal behavior was not present in the cross-fostered females, so the behavior of the young was more normal. These papers demonstrating that rat mothers can influence the behavior of their young postnatally have long gone unnoticed; however, they have important implications for research programs that desire to work with FSL rats but are required to rid them of nuisance viruses (parvovirus) or other infections (e.g., pinworm). The typical procedure is to impregnate FSL and parallel control rats and transfer the FSL pups to the control dams at the time of birth, usually by cesarean derivation. On three separate occasions, the exaggerated immobility phenotype was lost, making it difficult to test novel compounds. In one case, the colony was followed and it was determined that the phenotype had largely returned by the third generation (D. H. Overstreet, unpublished observations).

## VII. Recent and Current Research

Well over 20 publications have appeared on the FSL rat in the last 2 years, so it is reasonable to suggest that the rats are continuing to produce. This great

productivity was made possible by sending breeding nuclei for the establishment of colonies of the rats in Israel, Sweden, Greece, Denmark, South Africa, and Australia. There are also three breeding colonies in the United States, one of which is used solely to provide FSL rats to interested investigators. Highlights from these research groups will be presented in the remainder of this section and are summarized in Table 3.

*A. Israel.* Dr. Yadid and colleagues have been using the FSL rats to test whether physical means of antidepressant treatments would be effective. For example, it was determined that deep brain stimulation had an AD-like effect in the FSL rat (Friedman et al., 2012). Earlier, they have shown that stem cell injections also had an AD-like effect (Tfilin et al., 2010). Through collaborators in England, Yadid has examined elevations in arachidonic acid in the FSL rats (Green et al., 2009).

*B. Sweden.* Mathé has entered into a collaborative research arrangement with colleagues in Italy. This large group of highly skilled researchers has produced a number of exciting reports on the FSL rats. A key to the success of many publications is the research design. Not only have they included the intact FSL and FRL rats (the genetic component), but they also included another variable that has been associated with depression: early maternal separation (environmental factor). This powerful design has permitted some intriguing conclusions.

Their articles have challenged the theory that brain-derived neurotrophic factor (BDNF) is intimately related to depressed-like behavior. They reported that chronic treatment with several antidepressants

(citalopram, nortriptyline) had AD-like effects in the FSL rats but did not alter hippocampal BDNF levels (Hansson et al., 2011; Petersén et al., 2009). The current theory would predict that the levels of BDNF should increase in the hippocampus after chronic antidepressant treatment. Previous research on neuropeptide levels in rats subjected to ECS, a very effective antidepressant treatment, failed to detect altered levels of BDNF; however, the levels of nerve growth factor were increased (Angelucci et al., 2003).

Other studies have used proteomic strategies to develop a global pattern of changes in the FSL rat after chronic antidepressant treatment and/or early maternal separation (Piubelli et al., 2011a,b,c,d; Carboni et al., 2010). The results are extremely complex, but in sum, differences were reported to be dependent upon both the genetic factor (strain differences) and to the environmental factor (maternal deprivation) (Carboni et al., 2010).

Interestingly, glutamatergic signaling was found to be impaired in a recent study using in vivo amperometry. A significant increase in resting glutamate levels was observed in the 12- to 15-month-old FSL rats compared with the 3- to 6-month-old FSL rats and age-matched FRL rats on days 3–5 postimplantation of the detection electrode (Hascup et al., 2011). In the same study, significant fluctuations in resting glutamate (glutamate transients) were observed in FSL rats compared with FRL rats (Hascup et al., 2011). In a recent study from another group in Sweden, whole-cell recordings showed baseline glutamatergic synaptic transmission was higher in FSL rats than in SD rats (Gomez-Galan et al., 2012). In addition, impaired long-

TABLE 3

Highlights of current/recent work on FSL rat

Investigator	Country	Significant Findings	References
Yadid	Israel	Deep brain stimulation is AD-like	Friedman et al., 2012
Yadid	Israel	Implant of stem cells is AD-like	Tfilin et al., 2010
Yadid	Israel	FSL rat has increased arachidonic acid	Green et al., 2009
Mathé	Sweden	No agreement of behavior with BDNF	Angelucci et al., 2003; Petersén et al., 2009; Hansson et al., 2011
Mathé	Sweden	Proteomics reveal complex effects	Carboni et al., 2010; Piubelli et al., 2011a
Wegener	Denmark	Involvement of nitric oxide	Wegener et al., 2010
Wegener	Denmark	Cardiovascular and diabetes	Solskov et al., 2010
Wegener	Denmark	Feeding fat diet is depressogenic	Abildgaard et al., 2011
Wegener	Denmark	Studies on VEGF and BDNF	Elfving et al., 2010a,b
Wegener	Denmark	Studies on neuropeptide S	Wegener et al., 2012
Wegener	Denmark	Studies on synaptogenesis	Chen et al., 2010, 2012
Wegener	Denmark	Studies on ECT and brain morphology	Kaae et al., 2012
Wegener	Denmark	Social isolation and depressed phenotype	Fischer et al., 2012
Pilowsky	Australia	Cardiovascular changes related to 5-HT	Padley et al., 2005; Hildreth et al., 2008
Irvine	Australia	FSL rat is more sensitive to ecstasy	Jaehne et al., 2011
Daifoti	Greece	Differences in metabolizing enzymes	Kotsovolou et al., 2010
Daifoti	Greece	Sex differences	Kokras et al., 2009
Harvey	South Africa	Phosphodiesterase-5 inhibitors	Liebenberg et al., 2010
Diksic	Canada	Differences in serotonin synthesis	Hasegawa et al., 2006; Kanemaru et al., 2008, 2009; Nishi et al., 2009a
Diksic	Canada	Differences in other 5-HT variables	Nishi et al., 2009b; Satoh et al., 2011; Kovačević et al., 2010
Diksic	Canada	Differences in glutamate system	Kovačević et al., 2012
Diksic	Canada	Differences in brain glucose utilization	Kanemaru and Diksic, 2009

ECT, electroconvulsive therapy; VEGF, vascular endothelial growth factor.

term potentiation induced by high-frequency stimulation in hippocampal slices was seen in FSL rats compared with SD rats. These two observations support the importance of glutamate in depressive-like psychopathology (Gomez-Galan et al., 2012).

*C. Denmark.* Dr. Wegener and colleagues initially obtained the FSL rats to test the hypothesis that nitric oxide (NO) pathways might be involved in the depressed-like behavior of FSL rats. The studies observed that NO signaling is increased in depressed subjects, in particular during stress (Wegener et al., 2010). Because of the physiochemical nature of NO (being reactive due to an unpaired electron), this aspect be important in the internal well-being of the brain environment (for a review, see Wegener and Mathé, 2011).

Having a productive breeding colony, Wegener and colleagues expanded their research to look at several different topics. Adding to the hypothesis that neurotrophic factors may be related to the pathophysiology of depression, they found that the expression of BDNF and vascular endothelial growth factor were significantly decreased in the FSL rats compared with FRL rats in several brain regions (Elfving et al., 2010a,b). On an ultrastructural morphologic level, and using design-based stereologic methods, the researchers investigated hippocampal volume, neuron, and synapse numbers in the FSL and FRL rats following chronic imipramine therapy (Chen et al., 2010). Consistent with findings on the neurotrophic factors, this group reported that both the volume and the number of neurons and synapses were significantly less in the FSL saline group compared with the FRL saline group, a feature which was reversed following imipramine treatment (Chen et al., 2010).

A recent study also demonstrated that 10 days of either electroconvulsive seizures or sham treatment (Kaae et al., 2012) produced differential effects on hippocampal parameters. The basal level of hippocampal volume and neuron number were significantly lower in FSL rats compared with FRL rats, and the FSL strain trended toward having more glial cells (Kaae et al., 2012). Importantly, the structural differences found between the sham-treated animals (FSL versus FRL rats) were counteracted by ECS treatment, which also normalized the behavior of the FSL rats (Kaae et al., 2012). ECS treatment significantly increased the number of glial cells in the hilus of the FRL rats, and with the same tendency for the FSL rats (Kaae et al., 2012). In another study, the number of mitochondria in region CA1 of the hippocampus was assessed. It was observed that FSL rats had a lower number and a larger mean volume of mitochondria compared with FRL rats, and chronic treatment with imipramine normalized these changes (Chen et al., 2012). These experiments illustrate the importance of using a disease model to study cell proliferation in

relation to the effects of treatments that could potentially be translated to human conditions; these studies were unable to detect differences in the control animals (SD or FRL rats) following intervention.

In another series of experiments, the role of neuropeptide S (NPS) in depressive-like behavior was investigated. It was shown that NPS only affected anxiety-like behavior but not depression-like behavior, suggesting that NPS is a substrate primarily involved in anxious behavior (Wegener et al., 2011). The role of epigenetic factors was investigated in a study on the possible role of epigenetic alterations in the promoter of P11 following antidepressant treatment. It was found that decreased levels of P11 were associated with higher DNA methylation in the promoter region of the prefrontal cortex of FSL rats than was seen in FRL rats. The hypermethylated pattern of the FSL rats was returned to levels seen in the FRL rats following chronic administration of the selective serotonin reuptake inhibitor escitalopram (Melas et al., 2011).

Finally, as several other conditions, including heart disease and diabetes, display a high comorbidity with depressive disorders in humans, the relationship between these conditions and depressed-like behavior in the FSL rat was investigated. When cardiac function was investigated, myocardial infarct size was found to be significantly larger in the FSL rats than in the SD rats following ischemia/reperfusion injury (Solskov et al., 2010). In the same study, it was also demonstrated that FSL rats were hyperinsulinemic, with a strong tendency toward increased levels of fasting glucose levels compared with SD rats (Solskov et al., 2010). Oral glucose tolerance testing has shown that metabolic stress induced by a high-fat diet leads to increase insulin levels in both FSL and FRL rat strains, but fasting blood glucose levels are significantly increased in FSL rats ingesting a high-fat diet (Abildgaard et al., 2011). The metabolic changes were associated with increased depression-like behavior in the Porsolt test and with cognitive impairment, but only in the FSL rats; these findings indicate that the FSL rat is suitable in translational interdisciplinary depression research.

Interestingly, in a recent study, it was observed that the behavioral differences between the FSL and FRL rats may disappear if both strains are subjected to social isolation from 5 weeks of age. The FRL rats develop a clear depressive-like phenotype in the forced swim test without any detectable changes in the already-high levels of the FSL rats (Fischer et al., 2012). Thus, the isolated FRL rats have swim test scores that are similar to both the control and isolated FSL rats. This study emphasizes the complex relationship between genetic and environmental factors.

*D. Australia.* Pilowsky and colleagues in Sydney were also interested in cardiovascular regulation in the FSL rat. Initial findings showed that both FSL and FRL rats displayed elevated heart rates and reduced



heart rate variability compared with SD rats (Padley et al., 2005). However, FSL rats exhibited reduced phrenic nerve firing frequency, longer baroreflex latency, and reduced baroreflex gain of heart rate and sympathetic nervous system activity compared with FRL and SD rats (Padley et al., 2005). These autonomic and respiratory abnormalities in the FSL rat could be a consequence of their cholinergic supersensitivity or some other neurotransmitter abnormality.

In a subsequent study, the group focused on the possibility that there was a serotonergic abnormality in cardiovascular regulation in the FSL rat. They challenged the rats with 8-hydroxy-2-(di-*n*-propylpamino) tetralin, a serotonin 1A receptor agonist. As expected, the FSL rats exhibited a greater hypothermic response than did the FRL or SD rats. However, there was no decrease in heart rate or arterial pressure in contrast to what was observed in the FRL and SD rats (Hildreth et al., 2008). These findings suggest abnormal serotonergic control of cardiovascular function in FSL rats.

Pilowsky shipped FSL and FRL rats to Irvine and colleagues at the University of Adelaide; for the first time in nearly 20 years, the FSL and FRL rats were in the city where they were initially developed. Irvine and his colleagues were interested in whether the FSL rat would respond differently from the FRL rat to drugs of abuse, particularly stimulants. Their first report indicated that the FSL rat was more sensitive than to the FRL rat to MDMA (ecstasy) (Jaehne et al., 2011). More recently, they have suggested that MDMA may have antidepressant properties, particularly after acute treatment (Majumder et al., 2011). The former finding is consistent with a large body of literature indicating that the FSL rat is more sensitive to the effects of a variety of drugs with different mechanisms of action. However, it is not consistent with a report that the FSL rat is less sensitive to the activity-inducing effects of cocaine, another stimulant (Fagergren et al., 2005). This apparent anomaly could be due to differences in the mechanism of action of the two drugs. More work is required to clarify the picture.

*E. Greece.* Investigators in Greece under the direction of Papadopoulou-Daifoti and Konstandi were interested in whether the FSL and FRL rats differed in their profile of metabolizing enzymes that could influence their sensitivity to drugs. Although there were minor variations in some enzymes, there were no major differences (Kotsovolou et al., 2010). An interest in sex differences also motivated the research of this group (Kokras et al., 2009, 2011; see review by Dalla et al., 2011).

*F. South Africa.* This group, led by Harvey and colleagues, learned of the FSL rats through collaborating with Dr. Wegener on NO research. It was a relatively simple matter for them to obtain breeding colonies, which they are now using to explore the

antidepressant potential of inhibitors of phosphodiesterase 5. In an earlier study they found that the ability of these inhibitors to have AD-like effects depended on cholinergic tone, with a blocker like atropine facilitating AD-like effects. Their study with the FSL rats confirmed this relationship but also demonstrated that chronic treatment with two phosphodiesterase inhibitors, sildenafil and tadalafil, induced anxiolytic effects (Liebenberg et al., 2010, 2012).

*G. Canada.* Dr. Diksic was interested in examining in further detail the serotonergic differences between the FSL and FRL rats. There had been occasional reports of differences in serotonergic function between the two strains in the past, but none was comprehensive. A key early finding was that the FSL rat had reduced synthesis of serotonin, a finding that paralleled observations in humans (Hasegawa et al., 2006). Synthesis rates also differed after treatment with citalopram, desipramine, or buspirone (Kanemaru et al., 2008, 2009; Nishi et al., 2009b), with the FSL rats showing a consistently lower rate of synthesis.

Dr. Diksic and colleagues also reported the following serotonergic changes in the FSL rats: 1) increased 5-HT<sub>1B</sub> receptors (Nishi et al., 2009a); 2) decreased 5-HT<sub>1A</sub> receptors (Sato et al., 2011); 3) greater ability of fluoxetine to reduce serotonin transporter expression (Kovačević et al., 2010); 4) increased brain glucose utilization (Kanemaru and Diksic, 2009), although it remains unclear how this observation relates to reports on serotonergic abnormalities; and 5) decreased levels of metabotropic glutamate receptor 5 compared with those observed in SD and FRL rats (Kovačević et al., 2012).

*H. United States.* Upon Dr. Overstreet's retirement from University of North Carolina at Chapel Hill, arrangements were made to transfer the breeding colony of FSL rats to Duke University under the supervision of Dr. Amir Rezvani. They are being maintained purely as a breeding colony to provide qualified researchers with subjects. Interested investigators may contact Dr. Rezvani by e-mail (azadi@duke.edu) with as much detail of planned experiments as possible. Dr. Loftis of the Oregon Health Sciences University obtained her animals from Duke to explore further the relationship between the immune and nervous systems (Wilhelm et al., 2012). Dr. Daws of the University of Texas at San Antonio, who earlier confirmed the elevation of muscarinic receptors in the FSL rats (Daws and Overstreet, 1999), obtained a group to study serotonin clearance dynamics in greater detail. Her first report indicated that the FSL rat has a reduced ability to clear serotonin from extracellular fluid in the hippocampus, consistent with their reduced level of serotonin transporter expression relative to control SD rats (Owens et al., 2011).

The FSL rat has been widely used over the past 2 years, and this trend seems likely to continue.

### VIII. Novel Hypothesis—Changes in Potassium Channels Underlie Depressed-like Behavior of FSL Rats

For some time, the FSL rat has been known to exhibit greater responses to drugs that are noncholinergic. Table 4 summarizes the results of studies using core body temperature as the dependent variable. Note that the drugs that produce a greater hypothermic response in the FSL rat have diverse mechanisms of action and that there appears to be no simple explanation for these diverse effects. It should also be emphasized that this pattern of results may apply only to core body temperature. For example, alcohol induces a greater hypothermic response in the FSL rat than in the FRL strain, but there are no differences in the sleep-inducing effects (Overstreet et al., 1990). Even more intriguing is the observation that apomorphine, a mixed dopamine agonist, induces greater hypothermia but reduced stereotypy in FSL rats, even at the same dose (Crocker and Overstreet, 1991).

A clue to the basis for these diverse effects came with the publication on G protein-coupled, inward rectifying potassium channel (GIRK) knockout mice in 2005 by Dr. Costa and his group (Costa et al., 2005). They reported that the knockout mice exhibited reduced hypothermic responses to virtually all of the drugs listed in Table 4. Furthermore, they presented a scheme by which all of the systems interacting with the drugs would feed into the GIRK channel. Drugs interact with selective receptors, but these receptors are linked to G proteins, which, in turn feed into the GIRK channels. A corollary of this hypothesis could explain the diverse hypothermic responses of the FSL rat. If the GIRK channel is overactive, then a greater response for each system feeding into the channel would occur. To test this, we looked at the hypothermic response to baclofen, a  $\gamma$ -aminobutyric acid-B agonist. The FSL rat exhibited greater hypothermic responses (D. H. Overstreet, unpublished observations).

Until recently, there were no data on potassium channel function in the FSL rats, either in the

hypothalamic areas that regulate core body temperature or in the areas of the hippocampus that may be involved in depressed-like behavior. However, there is a considerable amount of literature implicating potassium channels in depressed-like behavior (Lazary et al., 2011; Liou et al., 2009; Heurteaux et al., 2006). In particular, blockers of the GIRK channels are being considered as antidepressants (Lodge and Li, 2008; Tsai, 2008). This finding is consistent with the suggestion that a hyperfunctioning GIRK channel might be the basis for the depressed-like behavior of the FSL rat.

Indeed, a recent report has linked the increased sensitivity of the FSL rat to benzodiazepines, which was first documented over 20 years ago (Pepe et al., 1988), with a change in a potassium channel. The Italian investigators found that the FSL rat had higher expression of the  $K^+Cl^-$  co-transporter KCC2 without a change in benzodiazepine receptors (Matriciano et al., 2010). This finding could pave the way for additional studies on other potassium channels in the FSL rats. As previously speculated, an overexpressed potassium channel in key brain regions could account for the increased sensitivity to multiple receptors in the FSL rat.

### IX. Conclusions

The FSL rat model of depression has been widely used to test well-known and putative antidepressants, with great success. The depressive-like behavior is not accompanied by anxiety-like behavior, as measured by the elevated plus maze. However, the FSL rat engages in very little social interaction, which measures a different type of anxiety-like behavior than the elevated plus maze. In 2011, a tremendous number of publications arose from international laboratories, and the body of literature is expected to continue to grow. The FSL rat has been productive; it still is productive, and it will continue to be productive. This statement is supported by the observation that 12 publications on the FSL rats have appeared thus far in 2012.

TABLE 4

Drugs that produce greater hypothermic responses in the FSL rat				
Drug	Dose	Mechanism of Action	Degree of Hypothermia FSL/FRL	References
	<i>mg/kg</i>		$^{\circ}C$	
Oxotremorine	0.2	Muscarinic agonist	1.8–2.2/0.6–1.1	Pucilowski et al., 1991; Overstreet et al., 1992, 1998a; Daws and Overstreet, 1999
Nicotine	0.4	Nicotinic agonist	1.51/0.46	Dilsaver et al., 1991; Schiller and Overstreet, 1993
Apomorphine	0.5	Dopamine agonist	3.00/1.77	Crocker and Overstreet, 1991
Quinpirole	5	Dopamine D2 agonist	1.94/1.17	Crocker & Overstreet, 1991
8-OH-DPAT	0.5	5-HT1A agonist	5.12/2.36	Wallis et al., 1988; Overstreet et al., 1994
Baclofen	2.5	GABA-B agonist	1.53/0.96	*
Alcohol	1500	Mixed	2.14/1.42	Overstreet et al., 1990, 1996

8-OH-DPAT, 8-hydroxy-di-propylaminotetralin; GABA-B,  $\gamma$ -aminobutyric acid-B.

\* D. H. Overstreet, unpublished observations.

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## Authorship Contributions

Wrote or contributed to the writing of the manuscript: Wegener, Overstreet.

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