

# Behavioral Characteristics of Pharmacologically Selected Lines of Rats: Relevance to Depression

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## Abstract

This brief review discusses the behavioral consequences of two pharmacologically selected lines of rats. Flinders Sensitive (FSL) and Flinders Resistant (FRL) Lines of rats were selected on the basis of differential hypothermic and behavioral responses to the anticholinesterase, diisopropyl-fluorophosphate (DFP). FSL rats are more sensitive to the hypothermic effects of cholinergic, serotonergic, and dopaminergic agonists but less sensitive to the locomotor or stereotypic effects of dopamine agonists. FSL rats exhibit greater immobility in the forced swim test and reduced social interaction compared with FRL rats, but do not differ in saccharin intake, behavior in the elevated plus maze, or responses for rewarding brain self-stimulation. The exaggerated immobility and reduced social interaction are counteracted by chronic treatment with antidepressants. Because FSL rats were more sensitive to 5-HT<sub>1A</sub> receptor agonists, high (HDS) and low (LDS) 8-OH-DPAT-sensitive lines were selectively bred for differential hypothermic responses to the 5-HT<sub>1A</sub> receptor agonist, 8-hydroxy-2-(di-N-propylamino)tetralin (8-OH-DPAT). HDS rats were also more sensitive to the hypothermic effects of oxotremorine, a cholinergic agonist, but selection for this response did not diverge with later selection. HDS rats exhibited greater immobility in the forced swim test than LDS rats and this correlated response could be seen early in selection (generation 3). HDS rats also showed reduced social interaction compared to LDS rats, but did not differ in behavior in the elevated plus maze. These findings confirm that selection for hypothermic responses to pharmacological agents do have behavioral consequences, notably the production of depressive-like phenotypes, which can be counteracted by chronic antidepressant treatment. Because increased 5-HT<sub>1A</sub> receptor sensitivity was common to both selected lines (FSL and HDS), neurobiological processes dependent on this receptor could contribute to the abnormal behaviors that manifest in these rat lines and thus suggesting a mechanism underlying depressive behaviors in

humans. However, available human data are inconsistent with this hypothesis and suggest that other mechanisms underlie these behavioral abnormalities in HDS and FSL rats. These mechanisms as well as additional behavioral testing in these rat lines will be discussed.

## Keywords

**Diisopropylfluorophosphate (DFP), 8-Hydroxy-2-(di-N-propylamino)tetralin (8-OH-DPAT), Flinders Sensitive Line (FSL), Flinders Resistant Line (FRL) Rats, High and Low 8-OH-DPAT Sensitive (HDS & LDS) Rats, Muscarinic Receptors, 5-HT1A Receptors, Forced Swim Test, Social Interaction Test, Elevated Plus Maze, Depression, Anxiety**

## 1. Introduction

The current brief review discusses the development of two pharmacologically selected lines of rats and some of the behavioral consequences of the selected breeding. Flinders Sensitive (FSL) and Flinders Resistant (FRL) Lines of rats were selected on the basis of differential hypothermic and behavioral responses to an anticholinesterase agent, diisopropylfluorophosphate (DFP), in order to determine whether similar mechanisms might be involved in the tolerance, sensitivity, and resistance to such agents [1]. Serendipitously, over the ensuing years, it became clear that FSL rats are a putative rodent model of depression, with strong face, constructive and predictive validity [2]-[4]. Because FSL rats have increased sensitivity to the hypothermic response to 8-hydroxy-2-(di-N-propylamino)tetralin (8-OH-DPAT) [5] [6], interest in the potential involvement of the 5-HT1A receptor in their depressive phenotype was sparked. Subsequently, high (HDS) and low (LDS) DPAT-sensitive lines were selectively bred on the basis of their hypothermic responses to the serotonin-1A (5-HT1A) receptor agonist, 8-OH-DPAT [7]. Both FSL and HDS rats share some striking similarities, including greater sensitivity to cholinergic and 5-HT1A agonists, and both exhibit exaggerated immobility in the forced swim test relative to FRL and LDS rats. As discussed in this review, other behavioral characteristics relevant to a depressive-like phenotype also manifest. Consequently, both FSL and HDS rats may be considered putative animal models of depression and useful in the assessment of potential antidepressants.

## 2. FSL and FRL Lines

### 2.1. Initial Selection

Earlier work had shown that tolerance development to the anticholinesterase DFP was accompanied by reduced sensitivity to muscarinic agonists without a change in cholinesterase enzymes [1] [8]-[10]. Consequently, a selective breeding study was conducted to see if resistance and/or sensitivity to DFP would be accompanied by similar changes. Three variables were used to assess the effects of DFP (water intake, body weight, hypothermia) and selection was based on a combination of these effects [11]. Over the course of 8 generations, only a more sensitive line, the FSL rats, was developed; FRL rats were generally similar in response to randomly bred Sprague-Dawley (SD) rats, the strain used to develop the lines [11]. Thus, investigators in future experiments have used either FRL or SD rats as controls for FSL rats (e.g., [12] [13]) and sometimes experimenters used both FRL and SD rats (e.g., [12]).

### 2.2. Cholinergic Changes in Selected Lines

As expected, there were no changes in cholinesterase enzymes, but there were changes in muscarinic sensitivity, with the FSL rat being more sensitive to muscarinic agonists [15] [16]. These increased responses to muscarinic agonists are accompanied by increased muscarinic receptor binding in FSL rats [17] [18]. Later studies revealed that the FSL rat was also more sensitive to the hypothermic effects of nicotine [19] and had elevated nicotinic receptors [20]. Cross-breeding studies employing F1 and F2 crosses as well as F1 backcrosses to the parental lines established that the muscarinic responses involved both dominance and additive genetics, with an estimate of 3 or more genes involved [6] [21]. This finding suggests that additional factors besides muscarinic or nicotinic receptors might be involved in the increased receptor sensitivity.

### 2.3. Changes in other Neurotransmitter Systems

Because of previous studies suggesting that the cholinergic system interacts with other neurotransmitter systems and of the commonly held belief that these other neurotransmitter systems may be involved in depressive disorders, we explored whether there might be changes in these systems in FSL and FRL rats. Indeed, evidence for changes in 5-HT [13] [22]-[24], catecholamines [25]-[27], neuropeptide Y [28]-[31] and nitrous oxide [32] has been found. A fuller description of these changes can be found in a recent review [4]. These changes in multiple systems in FSL rats call into question the simple model of cholinergic supersensitivity predisposing FSL rats to depressive-like behavior, even though depressed humans are more sensitive to cholinergic agonists [33]. Of particular relevance to our present discussion is a cross-breeding study, which revealed increased 5-HT<sub>1A</sub> sensitivity of FSL rats was correlated with their exaggerated swim test immobility but neither of these variables was correlated with their increased cholinergic sensitivity [6].

There is other evidence that is inconsistent with the cholinergic supersensitivity model of depression. For example, lithium treatment produces a reduced sensitivity to cholinergic agonists in the FSL rat [34], however does not alter the exaggerated swim test immobility [35]. Bright light exposure also reduces cholinergic supersensitivity of the FSL rat [36] but is not considered to be an appropriate treatment for endogenous depression.

Furthermore, muscarinic antagonists are ineffective treatments in most studies of human depression [37] and do not alter swim test immobility in rodents [38]. These findings suggest that perhaps changes in nicotinic receptor sensitivity [39]-[41] or 5-HT<sub>1A</sub> receptor sensitivity [5] [23] [42] are more relevant to the depressive-like characteristics of the FSL rat. See discussion for an elaboration of this issue.

There has also been an interest in serotonin transporters in the FSL rat. The most commonly prescribed class of antidepressant drugs are selective serotonin reuptake inhibitors (SSRIs). SSRIs increase extracellular 5-HT by inhibiting 5-HT uptake via the high-affinity serotonin transporter (SERT). Like humans, FSL rats show antidepressant-like activity in behavioral tests following repeated SSRI administration, but not following an acute injection [3] [4]. A major challenge in the treatment of depression is reducing the delay to therapeutic benefit, which can often take weeks to months. FSL rats therefore provide a useful animal model to assay novel antidepressant compounds, and importantly, to compare time to onset of antidepressant-like activity with SSRIs. Recent studies suggest that low-affinity, high-capacity transporters for 5-HT, such as the organic cation transporter 3 (OCT3) and plasma membrane monoamine transporter (PMAT) may limit the therapeutic efficacy of SSRIs by limiting the increase in 5-HT that follows treatment with an SSRI [43]-[46]. Recent studies show that FSL rats have greater expression of OCT3 and PMAT in hippocampus compared to SD rats [47] [48]. Greater activity of OCT3 and PMAT to clear extracellular 5-HT in FSL rats may contribute to their depressive-like phenotype as well as the need for SSRIs to be administered chronically in order to produce antidepressant-like effects in the FST. Consistent with this view, decynium-22 (a blocker of OCT3 and PMAT) produced antidepressant-like effects in FSL rats after an acute injection [48]. This behavioral effect was paralleled by greater inhibition of 5-HT clearance in hippocampus of FSL rats following decynium-22, compared with SD rats [48].

In addition to 5-HT, OCTs and PMAT can transport norepinephrine and dopamine [49], neurotransmitters that have also been implicated in depression and its treatment. Thus, the antidepressant-like activity of decynium-22 in FSL rats might also be attributed to increased extracellular norepinephrine and dopamine. Relevant to this argument is the observation that antidepressant-like effects in FSL rats could be seen after just 5 days of chronic treatment with desipramine, but not with fluoxetine [50]. Future studies will address these possibilities. To date, however, these data support the utility of FSL rats as a model of depression that can be used to explore new targets, such as OCTs and PMAT, for the development of more rapidly acting antidepressant drugs.

### 2.4. Behavioral Characteristics

Initial characterization of the FSL rat focused on increased sensitivity to cholinergic agonists and exaggerated swim test immobility [2]. Since that time, a number of other behavioral tests have been conducted, including an early demonstration that FSL and FRL rats did not differ in their performance in the elevated plus maze, a finding that suggested a lack of anxiety-like behavior in FSL rats [51]. A summary of the behavioral/physiological differences and similarities of FSL and FRL/SD rats is given in **Table 1**.

Once the similarity between FSL rats and depressed humans in regard to their muscarinic supersensitivity was recognized, several behavioral/physiological studies relevant to depression were carried out, as shown in the upper half of **Table 1**. The increase in Rapid Eye Movement (REM) sleep was one of the first parameters to be

determined in FSL rats [12] and this finding was replicated in the laboratory of a different investigator later [52]. A similar abnormality has been well established in depressed subjects (see [12] [52]) Based on earlier studies on depressed subjects, a phase advance of the circadian rhythm was predicted for FSL rats. Two studies confirmed this prediction [53] [54], and later studies in humans have confirmed parallel abnormalities in circadian rhythms in depressed patients [55] [56]. FSL rats were also shown to have similar impairments in immunological functions to depressed individuals [57] [58]. Most recently, a microarray analysis of hippocampal brain tissue revealed an abnormality in the adipocytokine signaling pathway in the FSL rat compared to the SD rat; a similar abnormality in humans with depressive symptoms has been suggested [59].

Given the great interest currently in neuroimmune systems in neuropsychiatric disease, including depression, and addiction [60]-[62], it might be a fruitful endeavor to examine normal and environmentally or pharmacologically challenged FSL rats to further probe novel cytokine-based mechanisms that may impact their abnormal behaviors. This point is underscored by the observations that stress is a risk factor in both addiction (relapse) and depression, and stress increases neuroimmune markers peripherally as well as in brain [63]-[66].

Another set of experiments sought to explore whether FSL rats exhibit anhedonia, one of the key symptoms of depression. Under baseline conditions, FSL rats did not differ from FRL rats for either saccharin intake [67] or the threshold for rewarding brain electrical self-stimulation [68]. However, when chronic mild stress was

**Table 1.** Behavioral and physiological characteristics of FSL and FRL rats.

Parameter	Difference	References
Muscarinic		
Sensitivity	FSL > FRL	[1] [6] [15] [16]
5-HT1A		
Sensitivity	FSL > FRL	[6] [7] [23] [42]
REM <sup>a</sup> Sleep	FSL > FRL	[12] [52]
Circadian Rhythm	FSL < FRL	[53] [54]
Immune Function	FSL < FRL	[57] [58]
Adipocytokine		
Signaling	FSL < FRL	[59]
Saccharin Intake	FSL = FRL	[67]
Rewarding Brain		
Self-Stimulation	FSL = FRL	[68]
Active Avoidance	FSL < FRL	[69]
Appetitive		
Learning	FSL = FRL	[70]
FST <sup>b</sup> Immobility	FSL > FRL	[6] [71]-[77]
Social Interaction	FSL < FRL	[74] [75] [77]
Elevated Plus		
Maze	FSL = FRL	[51]
General Activity	FSL = FRL	[51] [75] [77]
Acoustic Startle	FSL < FRL	[14]
Maternal		
Behavior	FSL < FRL	[78]
	FSL < SD	[79]

<sup>a</sup>Rapid eye movement; <sup>b</sup>Forced swim test.

employed, FSL rats exhibited a much greater decrease in saccharin intake than FRL rats [67]. Thus, for anhedonia, depressive-like behavior of FSL rats was revealed only when subjected to stress. A similar interpretation might be invoked to account for the findings of two other studies. When active avoidance learning was examined, FSL rats were impaired [69] but when appetitive learning was studied, FSL and FRL rats performed similarly [70]. A likely explanation for these different outcomes is that the shock stimulus used in the active avoidance paradigm is a stronger stressor than that associated with water deprivation used in the appetitive learning paradigm, again underlining a stress  $\times$  gene interaction in terms of precipitating anhedonia in FSL rats.

To some degree, the exaggerated immobility of FSL rats in the forced swim test (FST) (e.g., [6] [71]-[77]) may be accounted for by their greater sensitivity to stressors. It has been commonly assumed that this exaggerated immobility is a sign of depressed-like behavior, in part because it can be counteracted by chronic antidepressant treatment (e.g., [71]-[77]). However, this conclusion is weakened by evidence that antidepressant treatment may also have anxiolytic effects. Consistent with this view, lower social interaction behavior in FSL rats is also counteracted by chronic antidepressant treatment (e.g., [74] [77]). However, the situation is even more complicated, because FSL rats do not differ from FRL rats in either total entries or entries into open arms of the elevated plus maze, another test of anxiety-like behavior [51]. Thus, the “basal anxiety” level of FSL rats does not appear to differ from FRL rats. In addition to providing a measure of anxiety, low levels of sociability in the social interaction test may also be reflective of depressive-like behavior (see [4] [80]). One might speculate that the social interaction test is more stressful than the elevated plus maze test, revealing a differential response between FSL and FRL rats in the social interaction test. In any case, activity-related measures in the two tasks do not differ in the two lines (**Table 1**; [51] [77]).

For most tasks that have included SD rats in the comparison, FRL rats have performed similarly to SD rats. When differences have emerged, as in the forced swim test, the FSL rat has differed from the other two. However, when the acoustic startle test was employed, FRL rats differed from SD and FSL rats, which did not differ from each other [14]. The implications of this finding are not immediately apparent, although it is intriguing to consider that this test has often been used in modeling schizophrenia (see [14] [70]). If so, then we can conclude that the FSL rat, whose behavior is not different from the SD rats, is not a model for schizophrenia.

Two studies have reported that maternal behavior of FSL rat dams is impaired [78] [79]. Cross-fostering of FSL pups to FRL dams resulted in a reduction of immobility in the forced swim test as adults, but cross-fostering of FRL pups to FSL dams did not change immobility scores [78]. Thus, rearing FSL pups by the normal FRL dams has an antidepressant-like effect.

A few studies have suggested that the FSL rat shares similarities with some of the psychogenetically selected lines of rodents. Its reduced performance in the active avoidance test [69] suggests that the FSL rat may share some similarities with the Roman Low Avoidance (RLA) rat, which was selectively bred for low performance on this task (see [80]). Earlier studies provided some support for this, when it was found that RLA rats were more sensitive to cholinergic agonists in a complex maze compared to Roman High Avoidance (RHA) rats [81]. However, unlike FSL and FRL rats, there were no differences in muscarinic receptor binding between RLA and RHA rats [82]. More recent studies have shown that RLA rats, like FSL rats, are more immobile in the FST than RHA rats and that this immobility can be counteracted by chronic treatment with antidepressants [83] [84].

Another series of studies have compared the FSL rat to the Wistar Kyoto (WKY) rat, which was selectively bred as the normotensive control in a selective breeding study for hypertension and later found to have a variety of disturbances of emotional behavior (see [80]). These studies confirmed that WKY and FSL rats were both more immobile in the FST than their control counterparts (Wistar and FRL), but the WKY rat also exhibited reduced reward-related behavior and greater anxiety [85]-[88]. The H/Rouen mice, selectively bred for increased immobility in the tail suspension test, resemble the FSL rat in exhibiting increased REM sleep and a greater effect of muscarinic agonists on REM sleep [89]. However, there were no differences in 5-HT<sub>1A</sub> agonist-induced suppression of REM sleep [89] and the H/Rouen mice exhibited both depressive-like and anxiety-like behaviors on a variety of tasks [90]. Thus, both the WKY rat and the H/Rouen mouse may model a more severe depression with comorbid anxiety, whereas the FSL rat may model less severe depression without comorbid anxiety. Further tests of anxiety-like behavior in the FSL rat are required to substantiate this conclusion.

### 3. HDS and LDS Lines

#### 3.1. Initial Selection

As discussed, the FSL rat was found to be more sensitive to 5-HT agonists than the FRL rat [5] [23]. Moreover,

exaggerated immobility in the forced swim test was correlated with 5-HT sensitivity but not cholinergic sensitivity [6]. Consequently, a selective breeding study was conducted using 8-OH-DPAT, a selective 5-HT<sub>1A</sub> receptor agonist. A genetically heterogeneous rat strain, established by the interbreeding of 8 inbred strains, was obtained from the National Institutes of Health Heterogeneous Stock colony [2]. Once established, rats were challenged with 8-OH-DPAT at puberty (30 days) and core body temperature was recorded 30 min later with a rectal probe. The ten males and females showing the greatest decrease in temperature were used to establish the high “DPAT” sensitive line (HDS), while the ten males and females showing the least decrease in temperature were used to establish the low “DPAT” sensitive line (LDS). The remaining rats were inter-mated to establish the randomly selected line (RDS). Mating strategy avoided brother-sister breeding and took place at about 70 days of age, after the rats were subjected to the forced swim test. At about 35 days of age, the hypothermic response of rats to either 8-OH-DPAT or the cholinergic agonist, oxotremorine, was recorded (30 min after drug administration). There was a bidirectional rapid selection for the differential hypothermic effects of 8-OH-DPAT, with the HDS rats exhibiting a 0.5°C greater drop than the RDS rats and the LDS being (0.5°C lower by the 3<sup>rd</sup> generation). There was also a smaller but significant difference in the response of LDS and HDS rats to cholinergic agonists, which became larger with increasing generations [5]. A follow-up study revealed that the HDS rats became even more sensitive to 8-OH-DPAT over generations, with a decrease in core body temperature up to 4°C compared to 1.3°C - 1.9°C for RDS rats, and 0.5°C for LDS rats [91].

### 3.2. Serotonergic Effects

The hypothermic response to 8-OH-DPAT was blocked by a 5-HT<sub>1A</sub> receptor antagonist but not a 5-HT<sub>7</sub> antagonist, a finding that confirmed that the hypothermic effects of 8-OH-DPAT were mediated by its action at 5-HT<sub>1A</sub> receptors rather than 5-HT<sub>7</sub> receptors [91]. Receptor binding studies revealed that HDS rats exhibited higher 5-HT<sub>1A</sub> receptor binding in cortical and limbic regions compared to RDS and LDS rats, but there were no differences in raphe or hypothalamic nuclei [91] [92]. Later studies using behavioral tests reflective of selective 5-HT receptor action showed that behaviors initiated by stimulation of 5-HT<sub>2</sub> or 5-HT<sub>3</sub> receptors did not differ between HDS and LDS rats, whereas a behavior reflective of 5-HT<sub>1A</sub> receptor stimulation did [93]. Furthermore, differences in 5-HT<sub>1A</sub> binding sites between HDS and LDS rats were confirmed and determined not to be related to changes in G proteins [93]. Thus, selective breeding for the hypothermic effect of 8-OH-DPAT has been quite selective for 5-HT<sub>1A</sub> receptors and is associated with elevated 5-HT<sub>1A</sub> receptors, but not in regions normally associated with regulation of body temperature (e.g., hypothalamus). Further evidence for the selectivity of 5-HT<sub>1A</sub> receptor sensitivity comes from *in vivo* microdialysis studies. There were no differences in baseline extracellular 5-HT but HDS rats showed a greater increase in extracellular 5-HT after fenfluramine, a 5-HT releasing agent [94].

### 3.3. Other Neurotransmitter Systems

The cholinergic system has been the only system explored in HDS and LDS lines to date. HDS rats have increased sensitivity to the hypothermic effects of oxotremorine, which appeared early in development of the lines [5] but did not show further separation with continued selection for 8-OHDPAT [91]. The fact that rats selected for cholinergic sensitivity are more sensitive to the hypothermic effects of 5-HT<sub>1A</sub> receptor agonists, while those selected for 5-HT<sub>1A</sub> receptor sensitivity are more sensitive to the hypothermic effects of muscarinic agonists suggests that some common factor beyond the receptors might be involved. Possible factors will be considered in the discussion (see [4])

### 3.4. Behavioral Characteristics

Initial studies focused on the FST because immobility in this test was correlated with hypothermic effects of a 5-HT<sub>1A</sub> receptor agonist in the FSL and FRL F2 progeny [6]. Likewise, differences in immobility occurred early on in the selection for 5-HT<sub>1A</sub>-induced hypothermic effects, with HDS rats being more immobile, as predicted [5]. Later studies confirmed the exaggerated immobility in HDS rats, indicative of a depressive-like phenotype. Surprisingly, HDS rats drank more saccharin in the sucrose preference test suggesting that these rats do not display anhedonia, a prominent feature of depression [91]. Sucrose intake by HDS rats was reduced to a greater extent by 8-OHDPAT treatment compared to LDS rats [91]. These findings, along with those from other

behavioral tests, are shown in **Table 2**.

Social interaction and behavior in the elevated plus maze are two tests of anxiety-related behavior. HDS rats exhibited reduced social interaction without a change in activity. HDS and LDS rats did not differ in either total entries or entries into the open arms of the elevated plus maze [95] [96]. Thus, the HDS rat, like the FSL rat, showed anxiety-like behavior on the social interaction task but not the elevated plus maze. To further characterize these rats the effects of intrahippocampal 8-OH-DPAT were studied. LDS but not HDS rats exhibited an anxiogenic effect in the social interaction test, while no effects of intrahippocampal 8-OH-DPAT were observed in the elevated plus maze [95]. Acute fluoxetine treatment had similar anxiogenic effects in the social interaction test, without effects in the elevated plus maze [96]. On the other hand, chronic fluoxetine treatment did not affect behavior in the social interaction test, but had an anxiogenic effect in HDS rats in the elevated plus maze [96]. Furthermore, the intrahippocampal effects of 8-OH-DPAT were not altered after chronic fluoxetine treatment, suggesting that sensitivity of the 5-HT<sub>1A</sub> receptor was not changed [96]. These findings are hard to reconcile with the increased sensitivity to 5-HT<sub>1A</sub>-receptor agonist-induced hypothermia [2] [91] and elevated 5-HT<sub>1A</sub> receptors [92] [93] in HDS rats.

Another study employed the acoustic startle response, with baseline results being similar to those for FSL and FRL rats [14]. Like FRL rats, LDS rats exhibited an increased response to the tone [97]. However, the conditioned startle response was unaffected. Both 8-OHDPAT and buspirone increased startle in LDS rats but not HDS rats [97]. This increased effect in LDS rats does not seem to be consistent with the increased hypothermic sensitivity to 8-OH-DAT and suggests that the increased sensitivity of HDS rats may be specific for hypothermic effects.

Another study provided evidence for a similar conclusion. To investigate possible anxiety-like behavior in HDS rats, a conflict task was employed. After water restriction, rats obtained water in a drinking tube that was electrified for some time periods. These periods were paired with a tone and resulted in a 10-fold suppression of drinking [98]. HDS rats received fewer shocks and drank less water under baseline conditions than LDS rats, a finding that suggested anxiety-like behavior [98]. Low doses of 8-OH-DPAT produced small increases in shocks received (anxiolytic effect), while higher doses produced a reduction in water intake; these effects were comparable in HDS and LDS rats [98]. Thus, while anxiety-like behavioral differences were seen in HDS and LDS rats, there was no differential anxiolytic effect of 8-OH-DPAT. The final study employed a differential reinforcement of low (DRL) rates of responding task because of earlier evidence showing this task to be sensitive to antidepressant treatments [99]. If the rat responds too often, its rate of reinforcement is reduced. The HDS rats responded at a high rate and thus had a lower reinforcement rate than LDS rats [99]. Both the HDS and LDS rats responded to 8-OH-DPAT with a decrease in response rate and an increase in reinforcement rate [99]. In contrast, desipramine, a well-known antidepressant, selectively increased reinforcement rate in both lines [99]. Since antidepressants increase reinforcement rates, it was thought that the “depressed” HDS rats might exhibit a reduced reinforcement rate, but this was not the case. It is likely that the DRL task is reflective of different aspects of behavior than the forced swim test, because the latter involves a larger degree of stress.

Behavioral characterization of HDS and LDS lines is not yet complete. It will be useful to have information about these lines on tasks that differentiated the FSL and FRL rats, such as REM sleep and circadian rhythms (see **Table 1**) or their response to chronic treatment with other antidepressants (e.g., [71]-[77]). Nevertheless, the HDS rats are quite similar to the FSL rats for virtually all of the behaviors that have been studied in both groups (compare **Table 1** with **Table 2**).

## 4. Discussion

Despite incomplete behavioral profiles of the two lines (FSL & FRL and HDS & LDS), there are some remarkable similarities, as presented in **Table 1** and **Table 2**. Both lines are more sensitive to the hypothermic effects of muscarinic and 5-HT<sub>1A</sub> receptor agonists (e.g., [5] [6] [15] [91]). However, while the increased muscarinic response in FSL rats is associated with increased muscarinic receptors in hypothalamus [17] [18], there is not an increase in 5-HT<sub>1A</sub> receptor binding in the hypothalamus of HDS rats [92]. Nothing is known about muscarinic receptors in the HDS rats, but there is evidence for reduced 5-HT<sub>1A</sub> receptor binding in FSL rats [100] [101]. Thus, the hypothermic supersensitivity of the FSL and HDS rats to muscarinic and 5-HT<sub>1A</sub> receptor agonists is not explained solely by increases in the respective receptors. Although gene expression profiling provided evidence for small increases in muscarinic receptor and 5-HT<sub>1A</sub> receptor genes in the FSL rat, much larger differences

**Table 2.** Behavioral characteristics of HDS & LDS rats.

Parameter	Difference	References
Immobility in FST <sup>a</sup>	HDS > LDS	[5] [91]
Saccharin Intake	HDS > LDS	[91]
Social Interaction	HDS < LDS	[94] [95]
Plus Maze	HDS = LDS	[91] [95] [96]
General Activity	HDS = LDS	[91] [95] [96]
Acoustic Startle	HDS < LDS	[97]
Conflict Task	HDS < LDS	[98]
DRL <sup>b</sup> Responses	HDS < LDS	[99]
DRL <sup>b</sup> Reinforcers	HDS > LDS	[99]

<sup>a</sup>FST = Forced swim test; <sup>b</sup>DRL = Delayed reinforcement of low rate.

were found for other genes [102].

Support for a muscarinic or 5-HT1A supersensitivity model of depressive disorders is further eroded by consideration of data from depressed humans. Muscarinic receptor binding is reduced in depressed individuals [103] and mention was made earlier about the lack of efficacy of antimuscarinic drugs as antidepressant [35]. However, there is some excitement arising from new papers suggesting a rapid antidepressant effect of scopolamine [104]. The hormonal response to 5-HT1A receptor agonists appears to be unchanged in depressed individuals [105] [106], while there are mixed reports about 5-HT1A receptor binding [107] [108]. So far, there have not been any studies on the hypothermic effects of muscarinic or 5-HT1A receptor agonists in humans, so we have no direct comparisons.

The dopaminergic system might be another candidate as an abnormal neurochemical system in FSL rats. FSL rats have elevated catecholamine levels in limbic regions and these levels are normalized by chronic antidepressant treatment [24]. FSL rats also fail to release dopamine in the prefrontal cortex when stressed by foot shock [26]. However, FSL rats show increased sensitivity to the hypothermic effects of dopamine D2 agonists but reduced sensitivity to the locomotor and stereotypic effects of these drugs [23] [109]. Furthermore, there were no differences in dopamine D2 receptor binding between FSL and FRL rats [4] [25].

Recently, it was suggested that the potassium channel, which is a tertiary component of the hypothermic responses to 5-HT1A and muscarinic receptor-induced hypothermia, could contribute to the supersensitivity in the FSL rat [4]. Such a model would also explain how the FSL rat is also more sensitive to the hypothermic effects of dopamine D2 receptor agonists [25]; see Overstreet and Wegener [4] for further discussion.

Nevertheless, it is clear that selective breeding for muscarinic or 5-HT1A-induced hypothermia has resulted in rat lines with remarkably similar behavioral profiles for the tests that have been conducted in both lines. Thus, the FSL and HDS rats are both more immobile in the FST, and exhibit reduced social interaction when compared to their control FRL and LDS counterparts (Table 1 and Table 2). On the other hand, there are no differences in general activity or entries into the open arms of the elevated plus maze. Saccharin intake does not differ in FSL and FRL lines under basal conditions (Table 1) but HDS rats drink more saccharin solution than LDS rats (Table 2). These patterns of behavior suggest that FSL and HDS rats may be regarded as models of mild depression with some symptoms of anxiety and an absence of anhedonia.

Another view is to regard FSL and HDS rats as depression-prone, with depressive-like symptoms only emerging when stressors are applied. Thus, the stress of water exposure in the FST elicits a very dramatic decrease in behavior, but the exposure to the putatively less stressful elevated plus maze does not. The reduction in responding in the active avoidance task by FSL rats [69] could also be viewed as a response to a stressor. In this regard, it should be mentioned that FSL rats responded at a reduced rate in the appetitive learning task although its accuracy of response did not differ from FRL rats [70].

Two biochemical studies in FSL and FRL rats are consistent with this view. When a foot shock was applied to FSL and SD control rats, SD rats exhibited a typical increase in dopamine in limbic cortical regions, but FSL rats did not [26]. When FSL and FRL rats were subjected to a one hour restraint stress, FRL rats exhibited an

adaptive increase in corticotrophin releasing hormone mRNA, but FSL rats did not [95]. Thus, the FSL rat is less capable of mobilizing systems involved in the reaction to stress and, consequently, exhibits impaired behavioral responses.

Recent studies in the National Institutes of Health heterogeneous stock (NIH-HS) rats, from which the HDS and LDS rats were developed, are of relevance here. By studying a large sample of these NIH-HS rats investigators were able to perform a correlational and factor analytical study on multiple behaviors in the elevated zero maze and open field activity. The analysis revealed that many of the behaviors could be grouped predominantly into one of two factors, one of which might reflect anxiety-like behavior [110]. Another study showed that NIH-HS rats and RLA rats exhibited both anxiety-like and depressed-like behavior and greater hormonal responses to the behavioral tasks [111]. Of particular interest to the present discussion are observations that low performance in the active avoidance task is associated with FST immobility [112] and high performance in the active avoidance task is associated with high acoustic startle responses [113]. This pattern of behavioral associations is exactly what FSL and FRL rats show (Table 1). More extensive behavioral testing of FSL and FRL rats using the tasks and behavioral measures performed in NIH-HS rats might reveal an even more intriguing pattern, particularly as related to anxiety-like behavior, for which there is currently mixed results in FSL and FRL rats. Extension of the study in F2 rats derived from an FSL and FRL cross [3] to include such behaviors may provide even more informative results. Another fruitful line of investigation would be to study the different psychogenetically selected lines [80] in the same behavioral battery and subject the data to a factor analysis, as was done with the different alcohol-preferring lines and strains [114]. It is also of interest to carry out the social interaction test in NIH-HS rats to see which behaviors in this task are associated with the previously recorded behaviors.

It must be emphasized that rodent models of complex behavioral constructs in humans are limited by the heterogeneity of symptoms that are used to form the constructs. Depressive disorders are diagnosed when individuals exhibit certain behavioral symptoms. These could include changes in appetite (up or down), activity level (usually down) and sleep (up or down). So-called atypical depression is associated with increased appetite and excessive sleeping, which is different from the reduced appetite and sleeping of the typical depressed individual. A rodent model cannot be expected to mimic all of the symptoms typically displayed by depressed individuals. However, it is suggested that the FSL rat is an adequate model of depression because it exhibits some behaviors that are reminiscent of symptoms in depressed humans. Clearly, it does not exhibit anhedonia under baseline conditions (Table 1), but it drinks less saccharin solution when subjected to chronic mild stress [67]. The fact that the exaggerated immobility of the FSL rat is reduced by standard and novel antidepressants [71]-[77] strongly supports the contention that the FSL rat is a useful animal of depression.

The FSL rat model is now well-established, with breeding colonies in Sweden, Denmark, Israel, South Africa, Australia, Canada and the US. See the recent review [4] to learn about recent research done in these regions.

While behavioral and physiological endpoints have been fruitful and dominant foci in the use of FSL and HDS rats in modeling human psychiatric conditions, a future focus on neuroanatomical characteristics would likely also be meritorious. In this regard, contemporary tools in circuit mapping and signaling control offer a potentially rich platform upon which to assess mechanisms of strain-dependent differences in behavior. Tools associated with optogenetic [115] and DREADD (designer receptors exclusively activated by designer drugs) [116] technologies and the viral constructs used to deliver them *in vivo* permit specific access to select neuronal populations and circuits to pursue neurobiological processes controlling behavior. Strong and typically rapid selective breeding of hypothermic, anxiety-like, and depressive-like behaviors in the lines described herein suggest that specific circuits (e.g., hypothalamic and cortical) and receptor/neurotransmitter systems (e.g., 5-HT1A and cholinergic) would be intriguing targets of future studies.

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