

Review

# Depressive-like behavior and high alcohol drinking co-occur in the FH/WJD rat but appear to be under independent genetic control

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## Abstract

This review will consider the evidence supporting the view that a specific substrain of Fawn-Hooded rat (FH/Wjd) exhibits co-occurring depressive-like behavior and high alcohol intake independently. First, the FH/Wjd rat is compared with other Fawn-Hooded substrains (FH/Har, FHH/Eur, FHL/Eur) and it is concluded that only the FH/Wjd rat is both highly immobile in the forced swim test and drinks substantial amounts of 5–10% alcohol voluntarily. Next it is demonstrated that the FH/Wjd rat fulfils many of the criteria proposed for an animal model of alcoholism (becomes tolerant, becomes dependent and expresses withdrawal symptoms, bar-presses for alcohol). Other literature in addition to the high swim test immobility suggests that the FH/Wjd rat may also be an animal model of depression (high basal corticosterone levels, blunted hormonal responses to serotonergic agonists). To study the phenotypes more closely an inbred strain (ACI/N) of rat that drank little alcohol voluntarily and exhibited considerable swimming in the forced swim test (i.e., low immobility) was obtained. A systematic intercrossing of the parental strains and the resulting F1 progeny was carried out to generate more than 800 F2s. Swim test immobility, alcohol intake and preference and saccharin intake are four of the 7 variables assessed in each of these rats. Using classical quantitative genetics methods, it was determined that these four phenotypes exhibited modest heritability and were influenced by multiple genes. Correlation coefficients between immobility and the other measures were near zero, whereas alcohol intake and preference were highly correlated ( $r = 0.9$ ) and alcohol and saccharin intakes were modestly correlated ( $r = 0.3$ ). A final study showed that chronic fluoxetine treatment counteracted the high immobility but did not affect alcohol intake, similar to human studies. These findings suggest that although depressive-like behavior and high alcohol intake co-occur in the FH/Wjd rat, they are independently regulated.

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**Keywords:** FH/WJD rat; Excessive alcohol intake; Exaggerated swim test immobility; Saccharin intake; ACI/N rat; Inbred rats; Intercrosses; Independent phenotypes

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## 1. Introduction

Although the large majority of rodents do not drink much alcohol voluntarily, a variety of high alcohol drinking (HAD) rat strains has been developed using selective breeding techniques (e.g. Colombo et al., 1995; Li et al., 1993; Murphy et al., 2002; Sinclair et al., 1989). In contrast, there are some well-known inbred mouse strains that voluntarily consume substantial amounts of alcohol (e.g., Bachmanov et al., 2002; Belknap and Atkins, 2001; Gill and Boyle, 2005; Phillips et al., 1998) and there are relatively few selectively bred mouse lines (Grahame et al., 1999, 2000). Thus, the genetics of alcohol drinking may be based upon different types of designs in rats and mice (e.g., Gill and Boyle, 2005; Carr et al., 1998). Those Quantitative Trait Loci (QTL) studies so far completed in the selectively bred rats have revealed only a small number of QTL (Bice et al., 1998; Carr et al., 1998; Foroud et al., 2003), partly because of a lack of polymorphic loci and partly because the lines were not inbred. Therefore, a fuller understanding of the genetics of alcohol drinking might be revealed if a QTL study of appropriate inbred rat strains were conducted. The present review summarizes the extensive behavioral data that have been collected in the alcohol-preferring inbred Fawn-Hooded (FH/Wjd) rat, its counterpart, the alcohol-nonpreferring inbred ACI/N rat, and their intercrosses.

Depression and alcoholism often co-occur in humans but it has been difficult to find a single treatment which is effective against both conditions (Pettinati, 2004). Interestingly, the FH/Wjd rat exhibits elevated corticosterone levels (Aulakh et al., 1993) and blunted hormonal responses to serotonergic agents (Aulakh et al., 1988) as observed in some depressed individuals (Holsboer, 1999; O'Keane and Dinan, 1991; Lesch et al., 1990). The FH/Wjd rat is also much more immobile in the forced swim test compared to the ACI/N rat (Rezvani et al., 2002). Thus, depressed-like behavior and HAD co-occur in the FH/Wjd rat. The present review will summarize evidence from pharmacological and genetic studies that support the view that the two co-occurring phenotypes are independent.

## 2. Will the real FH/Wjd rat stand up?

A breeding nucleus for the FH/Wjd rat colony was obtained from W. Jean Dodds of the New York Department of Health. She had been inbreeding these rats for 19

generations at that point, so they can be considered inbred. Early studies concentrated on alcohol intake and related measures in the two-bottle choice procedure. The FH/Wjd rat drank much more alcohol than an outbred Wistar rat, one of its progenitor strains (Rezvani et al., 1990, 1991). However, there began to appear studies (Hall et al., 1998a, b, 2000) on another FH strain that drank only modest amounts of alcohol (2–3 g/kg). The source of these rats was not from Jean Dodds' laboratory, but the National Cancer Institute (NCI). They were given to NCI by Gordon Harrington (1973), who had inbred them and termed them the Iowa Reactive (IR) rats. By comparing FH/Wjd rats with IR rats it was discovered that there were substantial differences between the FH/Wjd rats and the IR rats in almost every variable (Overstreet and Rezvani, 1996), including body weight (FH/Wjd rats weigh more), immobility (FH/Wjd rats are more immobile) and alcohol intake (FH/Wjd rats drink more). Thus, it was concluded that there is more than one inbred substrain of FH rats and that any phenotypic characterization of these rats must indicate their source (Overstreet and Rezvani, 1996).

Below is a short history of the FH/Wjd rats and their distribution (see Overstreet and Rezvani, 1996). In addition to the two inbred strains developed by Dodds (FH/Wjd) and Harrington (IR or FH/Har), an outbred colony was maintained by Ethel Tobach (Tobach et al., 1984). Some of these rats were shipped to Europe and Professor Provoost of Erasmus University in the Netherlands selectively inbred them to obtain the substrains with high (FHH/Eur) and low (FHL/Eur) blood pressures, respectively. We sent some FH/Wjd and FH/Har rats to Prof. Provoost in exchange for some FHH/Eur and FHL/Eur rats. A four-strain comparison revealed some interesting differences, as reported by Overstreet et al. (1999). For the purposes of this review paper we focus on just two measures. As illustrated in Fig. 1, all of the FH substrains drank some alcohol voluntarily, but the FH/Wjd strain drank substantially more than the other three strains. In contrast, FH/Wjd, FHH/Eur and FHL/Eur rats were all highly immobile in the forced swim test (Fig. 2). This different strain distribution pattern for alcohol intake and immobility was the first evidence suggesting independence between these two phenotypes.

These studies reinforced our decision to choose the FH/Wjd rat as the HAD strain in a QTL analysis of alcohol intake in rats. The choice of a non-drinking strain was

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