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Research report

Phenotypes associated with psychiatric disorders are sex-specific in a mutant mouse line

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ABSTRACT

Wnt1-Cre- and Wnt1-GAL4 double transgenic (dTg) mice are used to study neural crest cell lineages by utilizing either the Cre/loxP or the GAL4/UAS system. We have previously shown that these mice exhibit behavioral abnormalities that resemble certain behaviors of psychiatric disorders and histologic alterations in the cholinergic and glutamatergic systems in the brain. The objective of the current study was to extend the behavioral analyses in these mice and to determine whether there were any sex-specific differences in the prevalence or severity of these behaviors. In the present study, we demonstrate additional behavioral abnormalities in dTg mice, such as increased locomotor activity, decreased social behavior, and an increased frequency in vertical jumping. Of these, the proclivity for vertical jumping was observed only in male dTg mice. In contrast, MK-801 administration induced increased locomotion in only female dTg mice. Furthermore, the concentrations of prolactin in the sera and oxytocin in the hypothalamus were both reduced only in female dTg mice, compared to controls. These sex-dependent behavioral and hormonal abnormalities in the dTG mice suggest that the phenotype of certain psychiatric disorders may be influenced by both genetic and sex-specific factors.

1. Introduction

Several psychiatric disorders show differential prevalence or progression between males and females, and this phenomenon is poorly understood. Two common psychiatric disorders, schizophrenia and autism spectrum disorder (ASD), show such sex-related differences. Schizophrenia (MIM 181500) is a psychiatric disorder that affects approximately 1% of the population worldwide. Schizophrenia has a typical onset from late adolescence to early adulthood and is more prevalent in males than in females (ratio of 4:3) (Jablensky et al., 1992; Tandon et al., 2009). ASD is a psychiatric condition that arises in childhood and is classified as a neurodevelopmental disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013; Kim, 2009). ASD affects approximately 1 out of every 68 children and occurs more often in males than in females (ratio of 4:1) (Developmental Disabilities Monitoring Network Surveillance Year, 2010 Principal Investigators and Centers for Disease Control and Prevention (CDC), 2014). Major symptoms of ASD include deficits in social communication and exhibition of restricted and repetitive patterns of behavior.

Although schizophrenia and ASD are classified as two distinct psychiatric disorders, several previous reports have suggested that both arise during development due to unknown genetic alterations. In studies conducted in monozygotic twins, high concordance rates of 48% and 92% were observed for schizophrenia (Onstad et al., 1991) and ASD (Bailey et al., 1995), respectively. Additionally, rare copy number variations at numerous genetic loci are implicated in both disorders (Guilmatre et al., 2009). Furthermore, in 2009, Rapoport et al. (2009) reported that childhood onset schizophrenia is preceded by, and comorbid with, pervasive developmental disorders in 30–50% of all cases. Although these studies provide strong evidence for a genetic link for these disorders, the molecular alterations underlying the pathogenesis and sex bias of these disorders are complex and incompletely known.

We have previously reported pathologic and phenotypic abnormalities in Wnt1-Cre and Wnt1-GAL4 double transgenic (dTg) mice (Nakajima et al., 2013, 2014), including certain behavioral abnormalities consistent with psychiatric disorders, such as ASD and schizo-

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phrenia. The mice were originally generated as a deleter mouse line used to generate conditional gene knockouts specifically in neural crest cell lineages. In these mice, Cre recombinase and the GAL4 transcriptional activator were randomly integrated into an unknown genomic region and are expressed during early embryonic stages under the control of Wnt1 regulatory sequences (Rowitch et al., 1999). We previously showed that the dTg mice exhibit abnormal social and cognitive behaviors, such as reduced nesting behavior, increased locomotor activity, decreased reciprocal social interaction, and impaired short-term spatial memory (Nakajima et al., 2013). Furthermore, the dTg mice demonstrate a hypersensitivity to sound (Nakajima et al., 2014). The dTg mice show histologic abnormalities in neural crest-derived brain regions. These include irregularities in the cholinergic and glutamatergic habenulointerpedunclar fiber tracts that project from the medial habenular nucleus of the epithalamus to the interpeduncular nucleus of the midbrain tegmentum (Nakajima et al., 2013). Given that human psychiatric disorders exhibit a sex bias, we hypothesized that the dTg mice would also show sex-specific differences. In the present study, we explore additional behavioral abnormalities of the dTg mice and their relationship to sex, as well as sex-specific changes in hormones, which may contribute to these behaviors.

2. Results

2.1. Behavioral analyses

Locomotor activity in dTg mice was evaluated using the open field test. The total distance traveled was increased in dTg mice of both sexes, compared to controls. Based on the center entry index, dTg mice of both sexes also exhibited an increase in total locomotor activity (Fig. 1), which is consistent with previous results (Nakajima et al., 2013)..

We next conducted the social approach (three-chamber; Fig. 2A) test. In the first round, wild type (Wt) and dTg mice of both sexes spent a longer period of time around the wire coop with an unfamiliar mouse inside (Stranger 1), than with the empty wire coop (Fig. 2B and C). In the second round, Wt mice of both sexes exhibited a significant preference for a new mouse (Stranger 2) over the previous mouse (Stranger 1), whereas dTg mice of both sexes spent equal amounts of time in each quadrant area (Fig. 2D and E)..

During the course of breeding, we noticed that young male dTg mice had a propensity to jump vertically. To see if this behavior was significantly different from that observed in the controls, we measured the frequency of vertical jumps in both groups. We observed an approximate 8-fold increase in the number of vertical jumps performed by four-week-old dTg male mice (Fig. 3A). In contrast, dTg female mice did not exhibit this behavioral change (Fig. 3B)..

The NMDA antagonist MK-801 has been shown to stimulate

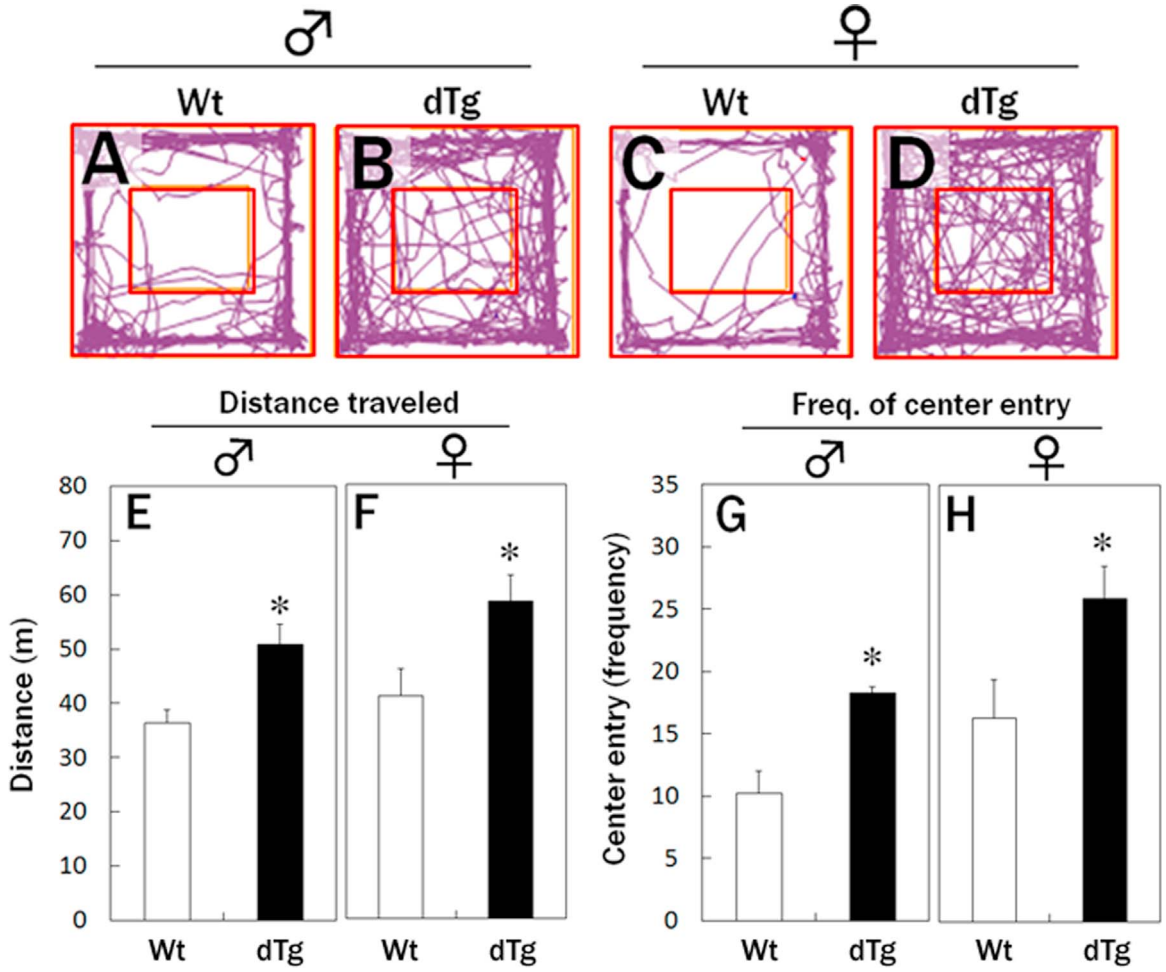

Fig. 1. Increased locomotor activity of double transgenic mice during the open field test. Total distance traveled and the number of entries into the center area were determined during an open field test. Representative images of video-tracked movements of wild-type (Wt) and double transgenic (dTg) male (A, B) and female (C, D) mice. (E) and (F) show the total distance traveled by male (Wt: n =4; dTg: n =4) and female mice (Wt: n =6; dTg: n =7), respectively. (G) and (H) are the total number of entries into the center area by male and female mice, respectively. *$p < 0.05$..

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