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Research Report

Deficits in odor-guided behaviors in the transgenic 3xTg-AD female mouse model of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is characterized by a number of alterations including those in cognition and olfaction. An early symptom of AD is decreased olfactory ability, which may affect odor-guided behaviors. To test this possibility we evaluated alterations in sexual incentive motivation, sexual olfactory preference, sexual olfactory discrimination, nursing-relevant olfactory preference and olfactory discrimination in female mice. We tested 3xTg-AD (a triple transgenic model, which is a "knock in" of PS1M146V, APPSwe, and tauP300L) and wild type (WT) female mice when receptive (estrous) and non-receptive (anestrous). Subjects were divided into three groups of different ages: (1) 4–5 months, (2) 10–11 months, and (3) 16–18 months. In the sexual incentive motivation task, the receptive 3xTg-AD females showed no preference for a sexually active male at any age studied, in contrast to the WT females. In the sexual olfactory preference test, the receptive WT females were able to identify sexually active male secretions at all ages, but the oldest (16–18 months old) 3xTg-AD females could not. In addition, the oldest 3xTg-AD females showed no preference for nursing-relevant odors in dam secretions and were unable to discriminate between cinnamon and strawberry odors, indicating olfactory alterations. Thus, the present study suggests that the olfactory deficits in this mouse model are associated with changes in sexual incentive motivation and discrimination of food-related odors.

1. Introduction

Different animal models of Alzheimer's disease (AD) have been engineered to examine amyloid-β (Aβ) and tau pathologies, and they support the hypothesis that a similar interaction occurs in human brain neurodegeneration (Lewis et al., 2001; Nelson et al., 2012). Among the lasting effects on cognition and behavior (Billings et al., 2007, 2005; LaFerla et al., 2007), it is well documented that olfactory alteration is one of the early symptoms in AD and provides an experimental tool to understand the mechanisms of synaptic dysfunction associated with the neuropathological progression (Wesson et al., 2010). The relation between olfactory perception and Aβ deposition in the olfactory system was

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studied in the Tg2576 APP transgenic AD mouse model that over-expresses a mutated form of the human Aβ precursor protein (Wesson et al., 2010). It has also been demonstrated that short-term passive, anti-murine-Aβ immunization can restore olfactory behavior after Aβ deposition (Morales-Corraliza et al., 2013; Wesson et al., 2013). Moreover, in APP/PS1 transgenic mice, the *locus coeruleus* degeneration exacerbates olfactory deficits (Rey et al., 2012). The triple transgenic mouse model (3xTg-AD) harboring the human APPSwe, PS1M146V, and TauP301L gene mutations displays an age-dependent accumulation of both intracellular Aβ and tau proteins mainly within the cortex, hippocampus, and amygdala (Oddo et al., 2003a). Studies of odor memory in this 3xTg-AD model revealed severe olfactory deficits without gross changes in Aβ and tau immunoreactivity in the olfactory bulbs (Cassano et al., 2011).

It is well known that in mice, scents play key roles in the recognition of food odors as well as in sexual behavior, where they mediate recognition of a member of the opposite sex as a potential mate. The main and the accessory olfactory systems respond to pheromones involved in social communication (Baum and Bakker, 2013; Chamero et al., 2012; Korzan et al., 2013).

Female mice gain olfactory information through both the accessory and main system, and these cues are essential to stimulate attraction to an individual male's scent (Hurst, 2009). The chemosensory system has important influences not only on sexual behaviors that are vital for reproductive success but also on the care of the offspring (Fraser and Shah, 2014; Keller and Lévy, 2012; Lévy and Keller, 2009). Mouse urine contains major urine proteins that bind to low-molecular-mass, volatile pheromones and protect them during their passage from the liver, and through the kidneys into the urine (Beynon and Hurst, 2003; Keller and Lévy, 2012). These volatile pheromones have profound effects on reproductive physiology and behavior (Tirindelli et al., 2009).

We designed this study to evaluate sexual incentive motivation, sexual olfactory preference, nursing-relevant olfactory preference and olfactory discrimination in transgenic (3xTg-AD) receptive and non-receptive females from 4 to 18 months of age. Females were chosen since the risk of AD is higher in females than in males.

2. Results

2.1. Sexual incentive motivation

The main objective of this behavioral test was to determine if 3xTg-AD female mice in estrous or anestrous showed a preference for a sexually active male or a sexually receptive female. The total distance traveled and velocity did not differ significantly between WT and 3xTg-AD mice at the ages studied (data not shown), indicating that these mice have no motor alterations. The sexual incentive motivation test showed that anestrous WT females at 4–5 months spent more time in the incentive zone of the female than that of the male ($\chi^2_{(7)}=17.66$, $P=0.003$) (Fig. 1a). WT females in estrous, at all ages, spent significantly more time in the male incentive zone than in the female incentive zone (Fig. 1b) ($\chi^2_{(7)}=23.98$, $P=0.0002$). Fig. 1c and d shows that 3xTg-AD females in anestrous and estrous at all ages studied (4–5, 10–11, and 16–18 months) showed no preference for either the male or the female (anestrous, $\chi^2_{(7)}=6.82$, $P=0.23$ and estrous, $\chi^2_{(7)}=10.6$, $p=0.59$).

2.2. Sexual olfactory preference

At 4–5 months of age, non-receptive female mice, both WT and 3xTg-AD, showed a significant preference ($\chi^2_{(7)}=21.34$, $P=0.007$) for the estrous female secretions (EFS) compared to clean bedding but no preference for sexually active male secretions (SAMS). This preference for the EFS persisted at 16–18 months of age only in the transgenic mice ($\chi^2_{(7)}=19.68$, $p=0.001$), as shown in Fig. 2a and e. At 4–5 months, both groups of mice in estrous showed a clear preference for SAMS ($\chi^2_{(7)}=26.64$, $P=0.001$) over clean sawdust and EFS (Fig. 2b). At 10–11 months, WT females preferred SAMS to EFS and clean sawdust ($\chi^2_{(7)}=21.34$, $P=0.007$), but 3xTg-AD females showed only a significant preference only for SAMS over clean sawdust (Fig. 2d). At 16–18 months of age WT females in estrous showed a significant preference for the SAMS sawdust ($\chi^2_{(7)}=25.31$, $P=0.001$), while 3xTg-AD females in estrous showed no preference (Fig. 2f).

2.3. Nursing-relevant olfactory preference

The main objective in this behavioral test was to determine if 18-month-old female WT or 3xTg-AD mice show a preference for dam secretions (DS). This age was chosen because at this time the AD pathology is clearly established. The WT females showed a statistically significant increase ($\chi^2_{(7)}=19.43$, $P=0.0002$) in the time spent with the DS compared with the clean sawdust, whereas 3xTg-AD females spent a similar amount of time smelling both types of bedding, as shown in Fig. 3.

2.4. Discrimination of food-related odors

At 4–5 months both groups (WT and 3xTg-AD) were able to discriminate cinnamon from strawberry ($\varepsilon^2_{(7)}=0.1227$, $P=0.002$), as shown in Fig. 4a. At 10–11 months of age, WT female mice significantly increased ($\varepsilon^2_{(7)}=0.0854$, $P=0.01$) the time spent sniffing a different odor, indicating that they were able to distinguish between new odors (saline from cinnamon, and cinnamon from strawberry), Fig. 4b. At 16–18 months of age they only discriminated between cinnamon and strawberry. On the other hand, 3xTg-AD mice were not able to discriminate between these odors at 10–11 or 16–18 months of age, Fig. 4c.

3. Discussion

The results of the present experiment indicate that 3xTg-AD female mice had a reduced sexual-incentive response to the sexually active male at all ages tested, which may be a consequence of diminished odor discrimination ability. This ability is sexually dimorphic and mostly of a motivational/sexual nature. Female WT mice respond more reliably than