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Research Paper

Hypersociability in the Angelman syndrome mouse model

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ABSTRACT

Deletions and reciprocal triplications of the human chromosomal 15q11-13 region cause two distinct neurodevelopmental disorders. Maternally-derived deletions or inactivating mutations of *UBE3A*, a 15q11-13 gene expressed exclusively from the maternal allele in neurons, cause Angelman syndrome, characterized by intellectual disability, motor deficits, seizures, and a characteristic increased social smiling, laughing, and eye contact. Conversely, maternally-derived triplications of 15q11-13 cause a behavioral disorder on the autism spectrum with clinical features that include decreased sociability that we recently reconstituted in mice with *Ube3a* alone. Based on the unique sociability features reported in Angelman syndrome and the repressed sociability observed when *Ube3a* gene dosage is increased, we hypothesized that mice with neuronal UBE3A loss that models Angelman syndrome would display evidence of hypersocial behavior. We report that mice with maternally-inherited *Ube3a* gene deletion (Ube3a^{mKO}) have a prolonged preference for, and interaction with, social stimuli in the three chamber social approach task. By contrast, interactions with a novel object are reduced. Further, ultrasonic vocalizations and physical contacts are increased in male and female Ube3a^{mKO} mice paired with an unfamiliar genotype-matched female. Single housing wild type mice increased these same social behavior parameters to levels observed in Ube3a^{mKO} mice where this effect was partially occluded. These results indicate sociability is repressed by social experience and the endogenous levels of UBE3A protein and suggest some social behavioral features observed in Angelman syndrome may reflect an increased social motivation.
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1. Introduction

Maternal deletions or loss-of-function mutations of the human gene *UBE3A*, located within the 15q11-13 chromosomal region, cause Angelman syndrome (AS), which is characterized by motor deficits, intellectual disability, and seizures (Matsuura et al., 1997; Kishino T. et al., 1997). Individuals with AS fall in the autism spectrum due to their repetitive-restrictive interests and profound language deficits (Peters et al., 2004a, b; Bonati et al., 2007; Moss et al., 2013). However, they also display a characteristic increase of smiling and laughter, increased proactive social contacts, and an amiable and gregarious personality, suggesting potentially hypersocial behaviors, opposite to those found in autism (Williams et al., 2006; Walz, 2007; Pelc et al., 2008; Adams et al., 2011; Heald et al., 2013).

Loss of maternal *UBE3A*, as found in Angelman syndrome, has previously been modeled in mice (Jiang et al., 1998; Miura et al., 2002). Mice with maternal *Ube3a* deletions (Ube3a^{mKO}) share several phenotypic characteristics with individuals with AS including decreased motor coordination, susceptibility to audiogenic seizures, and impaired learning and memory (Jiang et al., 1998). The penetrance of these behavioral phenotypes varies with genetic background and age (Huang et al., 2013). While aspects of the motor and intellectual deficits and the epilepsy observed in AS have been modeled in Ube3a^{mKO} mice (Jiang et al., 1998), behavioral features reflecting the distinct social phenotypes have not been reported.

Ube3a mRNA and protein are increased by neuronal activity *in vitro* and by exposure to environmental enrichment *in vivo* (Greer et al., 2010). In addition, early exposure to an enriched environment corrects several non-social behavioral phenotypes in Ube3a^{mKO} animals (Jamal et al., 2016). There is also evidence that prolonged single housing increases expression of Ube3a1 (but not 2 or 3) transcript with a unique 3′ UTR and encoding a truncated Ube3a protein lacking catalytic activity in rat brain (Valluy et al., 2015). Here we investigate the roll of *Ube3a* in experience-dependent regulation of social behaviors. We report that the duration of social interactions is prolonged and the paired ultrasonic vocalizations and physical contacts measured during exposure to a novel mouse are increased when the maternally-inherited *Ube3a* allele is deleted in mice to model the genetic defect found in Angelman

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syndrome. Loss of maternal *Ube3a* also largely blocks the suppressive effects of social experience on subsequent social behavior.

2. Materials and methods

2.1. Mice

Ube3a^{mKO} mice (JAXS, B6.129S7-*Ube3a*^{tm2Alb}/J) were backcrossed to FVB for 10 generations. Females positive for the deletion (unaffected mothers) inherited from their male parent were bred to wild-type males to produce mice designated p-Ube3a-mKO and their wild-type littermates. Females positive for the deletion (AS affected mothers) inherited from their female parent were bred to wild-type males to produce mice designated m-Ube3a-mKO and their wild-type littermate mice. Mice were housed in same-sex groups of ≤5 under standard laboratory conditions. Lights were on from 7 am to 7 pm and *ad libitum* food and water were available. Three chamber social approach, rotorod, and novel object tests were performed between 9 am and 5 pm. Paired ultrasonic vocalizations were recorded between 9 am and 12 pm. The testing arenas were cleaned with Clidox-S spray in between each mouse. Mice were given 1 h of acclimation to the testing environment prior to behavioral measurements. Prior to testing, mice were preconditioned to the experimenter by handling. All of the following tests were performed on breeding age female (6–13 weeks old) and male (8–13 weeks old) mice.

2.2. Testing order

Unique cohorts of mice were measured in multiple behavioral assays in the following orders. Female p-Ube3a-mKO mice: 1. three chamber social approach, 2. female-female paired ultrasonic vocalizations, 3. novel object preference, and 4. rotorod. Female m-Ube3a-mKO mice: 1. three chamber social approach, 2. female-female paired ultrasonic vocalizations, and 3. rotorod. Male p-Ube3a-mKO mice: 1. three chamber social approach, and 2. male-female ultrasonic vocalizations. The effects of social experience on three chamber social approach and paired ultrasonic vocalizations were measured in two unique cohorts of female m-Ube3a-mKO and wild-type littermate mice. For female p-Ube3a-mKO mice, the same cohorts were used to assess the effects of social experience on three chamber social approach and then, after a one week group housed period, the effects of social experience on paired ultrasonic vocalizations were measured.

2.3. Social approach test

Mice were placed in a clear acrylic box (50 × 100 cm) containing dividers with small (10 × 10 cm) doors to create a three-chambered enclosure. An overhead camera recorded activity and Ethovision software (Noldus) tracked mouse movement. Two small metal enclosures (inverted pencil holders, Office Depot) were placed in opposite corners of the arena and an Erlenmeyer flask filled with water was placed upon them to prevent mice from climbing to the top of the chamber. Test mice (wild type, p-Ube3a-mKO, or m-Ube3a-mKO) naïve to the arena were allowed to explore for 5 min and then removed to a holding cage. A novel sex- and age-matched non-littermate wild-type mouse was placed in one of the two small enclosures. The location of the novel mouse was alternated to control for any innate side preference. These probe mice were habituated to the small enclosures in 1 h sessions two a day for two days prior to testing. The test mouse was then returned to the cage and allowed to free-roam for two consecutive five minute trials while movements and the time spent in each third of the enclosure were automatically scored by Ethovision and the time sniffing the chambers was scored by a trained observer blind to genotype. The arena was evenly lit by an overhead fluorescent light source.

2.4. Rotorod

Motor function of p-Ube3a-mKO, m-Ube3a-mKO, and control wild-type littermate mice were tested using the rotarod (Ugo Basile A-Rod for mice). Each experiment was performed during the light phase inside a fume hood with an overhead fluorescent light. Mice were given two trials per day with a 60 min inter trial interval for 4 consecutive days. On each day we calculated the average time spent on the rotarod or the time until the mouse made three consecutive rotations on the rotarod. The duration of the trial was 5 min and the rod accelerated from 4 to 40 rpm. 10 mice per genotype were measured.

2.5. Social vocalizations

Female-Female Social Vocalization Test: Pairs of age- and genotype-matched, non-littermate, female mice were studied. Male-Female Social Vocalization Test: A wild-type or p-Ube3a-mKO male and an unfamiliar, sexually mature, wild-type female were studied. Mice were placed simultaneously (to avoid resident-intruder aggression) into a small novel clean 25.4 cm circular plastic chamber at room temperature inside an unlit sound isolation box for 5 min. Vocalizations were recorded with a condenser ultrasound microphone (Avisoft-Bioacoustics CM16/CMPA), an UltraSoundGate (Avisoft Bioacoustics 116Hb) and the Avisoft Recorder USGH software (Avisoft Bioacoustics). Avisoft-SASLab Pro software was used to quantify the number of vocalizations and the time spent vocalizing. The USV detection settings were: max frequency changes (3 pixels), frequency range limit (35–250 kHz), min whistle duration (10 ms), hold time (20 ms), min total duration (10 ms). Sampling rate is 250,000 Hz (at 976 Hz FFT size is 256 with 0% overlap). Simultaneous video recordings were made using a webcam mounted in the lid of the container. Physical interaction (direct contact) times were measured by a trained observer blinded to genotype.

2.6. Novel object

Mice were placed in a large (50 × 50 cm) open field lit from above by a fluorescent ceiling light and allowed to explore for 10 min. An overhead camera recorded activity and Ethovision (Noldus) was used to track mouse movement. Mobility in the open field was scored by the software. After 10 min a novel object (colored bottle cap) was placed into the open field near one corner and the time the mouse spend interacting with the object was scored by an observer blind to genotype for 5 min.

2.7. Statistical analysis

Multiple groups were compared by 2-way ANOVA with the Bonferroni post-test. Three chamber data was analyzed by a repeated measure 2-way ANOVA with the Bonferroni post-test. Ultrasonic vocalization and physical interaction data were analyzed using a two-tailed unpaired Student's *t*-test. Single groups were compared by 1-way ANOVA with the Bonferroni post-test.

3. Results

3.1. Prolonged social interest in Angelman syndrome mice in the three chamber social task

The three chamber social approach test was used to evaluate for a social preference in mice (Nadler et al., 2004). We evaluated adult female mice generated by breeding females positive for the deletion inherited from their male parent (unaffected mothers) bred to wild-type males to produce wild-type and p-Ube3a-mKO mice. A separate cohort, generated by breeding females positive for the deletion inherited from their female parent (AS mothers) to wild-type males to

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