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Research report

Genetic reduction of noradrenergic function alters social memory and reduces aggression in mice

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Abstract

Aberrant social behavior is a hallmark of many cognitive, mood, and neurological disorders, although the specific molecular mechanisms underlying the behavioral deficits are not well understood. The neurotransmitter noradrenaline (NA) has been implicated in some of these disorders, as well as in several aspects of social behavior in humans and animals. We tested dopamine β-hydroxylase knockout (*Dbh* −/−) mice that lack NA in various social behavior paradigms. *Dbh* −/− mice have relatively normal performance in the elevated plus maze, light/dark box, and open field test – three measures of anxiety – and a social recognition test. In contrast, *Dbh* −/− mice displayed a specific deficit in a social discrimination task and had a nearly complete absence of resident-intruder aggression. These results indicate that intact NA signaling is required for some types of social memory and aggression, but that a lack of NA does not greatly affect anxiety in mice. Further exploration of NA deficits in neurological disease may reveal mechanisms of aberrant social behavior.

Keywords: Noradrenaline; Dopamine β-hydroxylase; Anxiety; Aggression; Social memory; Social behavior

1. Introduction

Defects in the noradrenergic system have been implicated in many mood, cognitive, and neurological disorders that manifest abnormal social behavior, including attention deficit and hyperactivity disorder (ADHD), anxiety disorder, psychotic depression, and Alzheimer's disease. In addition, evidence has been mounting in recent years suggesting that noradrenaline (NA) also plays an important role in the regulation of several aspects of social behavior, including social anxiety [1,2], aggression [3,4], and social memory [5–9]. Therefore, an understanding of the contribution of NA to these behaviors may lead to a more detailed comprehension of neurological disease symptomology and treatment.

A strong connection between NA, anxiety, and other stress-related disorders has been previously established [1,2,10–14], although the valance of the interaction is the subject of some controversy. Stress increases the firing of locus coeruleus noradrenergic neurons and induces cortical and subcortical NA release, which is associated with anxiety-like behaviors. Interactions between NA and corticotropin-releasing factor (CRF) are thought to activate the nervous system in response to environmental challenge, and dysfunction of these systems is hypothesized to contribute to anxiety disorders. However, it is important to consider that, depending on neurochemical and environmental influences, activation of the noradrenergic system can be anxiolytic.

The ability to recognize familiar individuals, or social memory, is critical to the formation of social groups, reproductive behavior, and ultimately, species survival, and this type of memory is impaired in Alzheimer's disease. NA appears to be critical for some aspects of social memory. For example, lesions of the noradrenergic projections to the olfactory bulb in female mice before birth increase cannibalism of newborn pups [5], and genetically engineered female mice that lack NA show impaired maternal behavior, with most pups born to those mothers dying within a few days of birth [7]. Pharmacological depletion of central NA impairs the ability of adult rats to recognize a familiar juvenile,

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whereas pharmacological elevation of NA enhances social recognition [6,8,9]. These findings strongly suggest that noradrenaline plays an important role in regulating the formation of social memory.

The noradrenergic system also appears to be involved in aggressive behavior. For example, lesions of the noradrenergic system reduce aggression [15–18]. In addition, genetically engineered mice that lack α_{2C}-adrenergic autoreceptors, and consequently have increased NA levels, show enhanced isolation-induced aggression toward an unfamiliar intruder, whereas mice that overexpress these receptors show the opposite trend [19].

Because anxiety, social memory, and aggression all appear dependent on central NA, it is likely that NA is a critical element in the neural pathways that regulate social behavior in general. We hypothesized that mice with genetically reduced noradrenergic function will display abnormal social behavior. Specifically, we predicted that mice lacking NA would display reduced anxiety, impaired social memory, and low levels of aggression. To test these hypotheses, we examined these social behaviors in dopamine β-hydroxylase knockout (*Dbh* −/−) mice. DBH is the enzyme that converts dopamine to noradrenaline, and *Dbh* −/− mice lack the ability to synthesize NA and show a complete loss of noradrenergic function [20,21]. This model of NA depletion is especially relevant for human disorders because DBH activity is controlled by a polymorphism in the human *Dbh* gene [22].

2. Materials and methods

2.1. Animals

Dbh −/− mice, maintained on a mixed 129/SvEv and C57Bl6/J background, were developed and generated as previously described [19,20]. *Dbh* +/− mice have normal catecholamine levels and are indistinguishable from WT littermates for all previously tested phenotypes [7,21,23]. Therefore, heterozygous (*Dbh* +/−) littermates were used as controls for all experiments in this study. Male mice between 3 and 6 months of age were used for all experiments.

Experimental protocols were approved by Institutional Animal Care and Use Committee (IACUC) at Emory University and meet the guidelines of the American Association for Accreditation of Laboratory Animal Care.

2.2. Behavioral testing

Prior to behavioral testing, mice were group housed in polypropylene cages in the animal colony on a 12 light/12 dark cycle (lights on at 07:00). After measures of anxiety were completed, mice were separated and housed individually for at least 1 week prior to tests of social behavior and aggression. Three- to six-month-old male mice were tested in the following battery of behavioral tests in the order listed below. All testing was performed during the light phase. All behavioral tests were videotaped and scored at a later time by an experimenter blind to their genotype using the Ethom event-recording software (version 1.0 by Hsi-Te Shih).

2.2.1. Elevated plus maze

The elevated plus maze was comprised of two open arms (25 cm × 5 cm) and two closed arms (25 cm × 5 cm × 5 cm) that extended from a central platform (5 cm × 5 cm), and was elevated 40 cm from the floor. The apparatus was constructed of clear acrylic over which black duct tape was applied to the walls and floor, which prevented slippage on the open arms. Mice were placed individually in the center square facing an open arm and allowed to explore the maze for 5 min. An arm entry was counted only when all four paws were inside the arm. Measures scored included: (1) time spent in open arms, (2) time spent in closed arms, (3) number of open arm entries, (4) number of closed arm entries, and (5) number of rears in closed arms. Percent of time spent in open arms and total number of entries (to assess locomotor activity) were calculated from the raw data.

2.2.2. Light/dark test

The light/dark apparatus consisted of a rectangular clear acrylic box (30 cm × 14 cm × 14.5 cm), which was divided into two compartments. White paper was applied to the outside of the walls and floor of the light compartment (20 cm × 14 cm × 14.5 cm) and the top was left open. The walls and floor of the dark compartment (10 cm × 14 cm × 14.5 cm) were covered with black paper and had a roof constructed of black paper. A removable cardboard divider that contained a small square opening at floor level (5 cm × 5 cm) separated the two compartments. Testing was performed under fluorescent lighting. Mice were individually placed in the light side of the box, facing away from the dark compartment, and allowed to explore the apparatus for 5 min. Measures scored included: (1) latency to enter dark compartment, (2) latency to re-enter light compartment, (3) time spent in dark compartment, (4) time spent in light compartment, and (5) number of light to dark transitions.

2.2.3. Open field activity and investigation

The open field apparatus was a circular arena (96.5 cm diameter) with opaque gray plexiglass walls (28 cm high). A permanent marker was used to scribe a smaller circle 18 cm from the walls that divided the chamber into a smaller inner circle (area = ∼3100 cm^2) and an outer ring (area = ∼3800 cm^2). Within the inner circle were four small PVC cylinders (3.5 cm high, 3.5 cm diameter opening) in a random arrangement that were used to measure investigatory behavior of the mice. Mice were placed individually in the center of the inner circle and allowed to roam freely about the apparatus for 5 min. Measures included: (1) time spent in inner circle, (2) time spent in outer ring, (3) total number of crossings between the divisions, and (4) number of head pokes into the cylinders.

2.2.4. Social recognition

The social recognition test was performed as described [24]. All mice were individually housed for at least 1 week prior to social memory testing. For the 2 days prior to testing, mice were habituated to the stimulus animals (ovariectomized C57Bl6/J females). This was done to reduce the amount of sexual behavior exhibited by the males during testing. In trials 1–4, a stimulus animal (same animal for all four trials) was placed in the male's home cage for 1 min with 10 min intertrial intervals. On the fifth trial, a novel stimulus animal was placed in the male's cage for 1 min. Investigation time, which included sniffing and close following of the stimulus animal, was scored from videotape. Sexual behavior, such as mounting, was not included in investigation time. Using this method, familiarity or

social memory can be observed as a reduction in investigation time over the first four trials.

2.2.5. Social discrimination

Several days (3–7) after social recognition testing, mice were tested in the social discrimination paradigm. In the first trial, a stimulus animal (ovariectomized female) was placed into the male's home cage for 5 min and investigation time was measured. Thirty minutes later, the male was simultaneously exposed to the same stimulus animal from the first trial and a novel stimulus animal for 5 min. Social memory was assessed by comparing the amount of time the male spent investigating the familiar animal to the amount of time spent investigating the unfamiliar stimulus animal.

As a control for the social discrimination test, males were exposed to the same stimulus animal in two trials consisting of 5 min each with an intertrial interval of 30 min. Social memory was assessed by comparing the time spent investigating the stimulus animal in the second trial to investigation time in the first trial. This control occurred 3–7 days after social discrimination testing. The social discrimination test was also performed using females as both the test and stimulus animals.

2.2.6. Resident–intruder aggression

Males were housed individually for at least 1 week following social memory testing before aggression was assessed. Aggression was assessed over three sessions, spaced 2–3 days apart. Males were exposed to different C57Bl6/J intruder males in each session. An intruder male was placed in the subject male's home cage for 5 min. Measures included: (1) attack latency, (2) attack duration (total), (3) number of aggressive bouts, and (4) frequency of tail-rattling. Animals that did not attack the intruder were given an attack latency of 5 min. In addition, defensive behaviors, such as flight and defensive supine postures, were scored if observed.

2.3. Data analysis

Data from the anxiety experiments were analyzed using Student's *t*-tests when comparing groups of equivalent variance and the Mann–Whitney non-parametric test when comparing groups of unequal variance. Social recognition, social discrimination, and social memory data were analyzed by two-way ANOVA with genotype as a between-subjects factor and trial as the within-subjects factor. The Student–Newman–Keuls post hoc test was used to analyze main effects. Aggression data were analyzed by Fisher's exact test.

3. Results

3.1. Anxiety tests

To assess the role of NA in anxiety-like behavior, we tested the performance of *Dbh* +/− and *Dbh* −/− mice in three anxiety paradigms: the elevated plus maze, the light/dark box, and the open field test. For the elevated plus maze, no genotype differences were observed for total arm entries, percent open arm entries, or percent time in open arms, although *Dbh* −/− mice tended to spend more time in the open arms (Fig. 1). *Dbh* −/− mice had significantly fewer rears in the closed arms. Similarly, no genotype differences were observed in

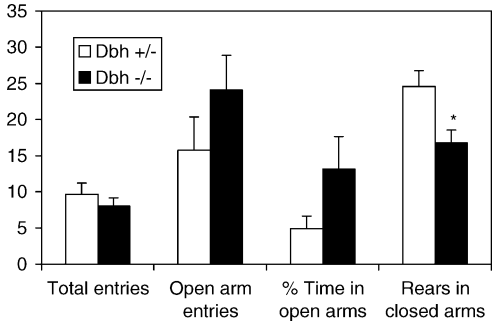

Fig. 1. Behavior of *Dbh* +/− and *Dbh* −/− mice in the elevated plus maze. Shown is the mean (±S.E.M.) for total arm entries, number of open arm entries, percent of total time spent in open arms, and number of rears in closed arms during the 5 min test. No significant differences between genotypes were found for any measure tested except number of rears in closed arms ($^{*}P < 0.01$). $N = 12$–13 per genotype.

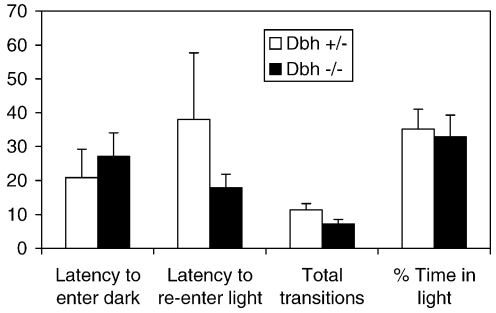

Fig. 2. Behavior of *Dbh* +/− and *Dbh* −/− mice in the light/dark box. Shown is the mean (±S.E.M.) for the latency to enter the dark compartment, the latency to re-enter the light compartment after first entering the dark compartment, total number of transitions between compartments, and percent of time spent in the light compartment during the 5 min test. No significant differences between genotypes were found for any measure tested. $N = 12$–13 per genotype.

the behavior of mice in the light/dark box (Fig. 2). Although the total number of crossings in the open field test was reduced in *Dbh* −/− mice, the percent time in the center field and number of investigatory head pokes was unchanged in knockouts (Fig. 3). Taken together, these results indicate that

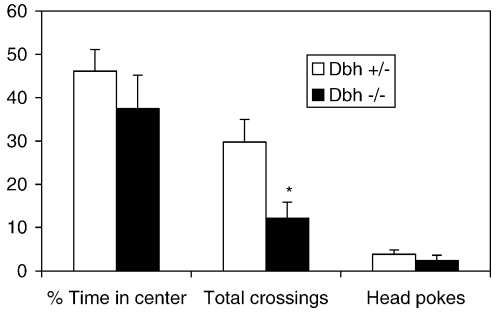

Fig. 3. Behavior of *Dbh* +/− and *Dbh* −/− mice in the open field test. Shown is the mean (±S.E.M.) for the percent of the total time spent in the center area, the total number of crossings between the center and outer areas, and the number of head pokes into the cylinders during the 5 min test. Only total crossings differed between genotypes ($^{*}P < 0.05$). $N = 11$–13 per genotype.

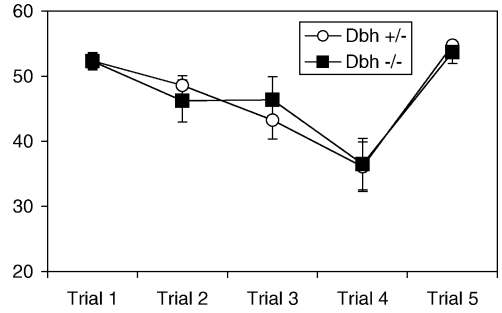

Fig. 4. Performance of *Dbh* +/− and *Dbh* −/− mice in the social recognition test. Shown is the mean (±S.E.M.) investigation time of the resident male of a stimulus female. For each resident male, the stimulus female used in trial 1 was reintroduced in trials 2–4, while a novel stimulus female was used for trial 5. No significant differences between genotypes were found. $N = 12–13$ per genotype.

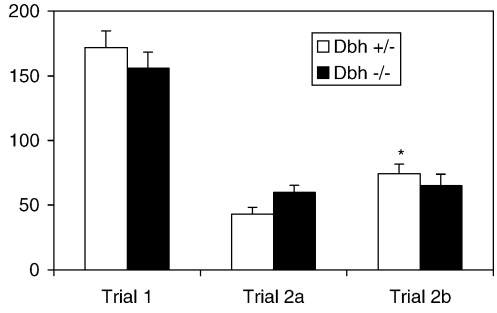

Fig. 5. Performance of *Dbh* +/− and *Dbh* −/− mice in the social discrimination test. Resident males were exposed to a stimulus female, and then were exposed to the same stimulus female and a novel stimulus female simultaneously 30 min later. Shown is the mean (±S.E.M.) investigation time of the resident male of the stimulus female during the pretest (trial 1), and the familiar stimulus female (trial 2a) and the novel stimulus female (trial 2b) 30 min later. *Dbh* +/− spent more time investigating the novel female during trial 2 ($^{*}P < 0.05$), but *Dbh* −/− mice did not. $N = 11–13$ per genotype.

a complete lack of NA does not grossly alter performance in standard anxiety paradigms in mice.

3.2. Social memory tests

Dbh −/− mice have profound defects in maternal and paternal behavior [7]. To determine whether these abnormalities extend to social interactions and social memory between adult animals, we tested *Dbh* +/− and *Dbh* −/− mice for social recognition and social discrimination. In the first test (habituation/dishabituation to a social stimulus), male *Dbh* +/− and *Dbh* −/− mice were exposed to a stimulus animal (ovariectomized C57BL6/J female; same animal for four trials) in the male's home cage for 1 min with 10 min intertrial intervals, and social investigation time was measured. On the fifth trial, a novel stimulus animal was placed in the male's cage for 1 min. There was a main effect of trial [$F(4, 115) = 14.86$, $P < 0.01$], but not genotype or genotype × trial (Fig. 4); males of both genotypes reduced investigatory time upon repeated exposure to the same stimulus female. Males of both genotypes also increased investigatory time when a novel female was placed in the cage after four trials with the same female (Fig. 4).

We next further challenged the social memory of the male mice by assessing their ability to discriminate between a familiar and novel female. A female was placed in the male's cage for 5 min, and investigation time was recorded. Thirty minutes later, the same female and a novel female were simultaneously placed in the male's cage, and interaction time with each female was recorded. There was a main effect of trial [$F(1, 44) = 131.97$, $P < 0.01$], and a strong trend for a genotype × trial interaction [$F(1, 44) = 3.49$, $P = 0.07$] (Fig. 5). While males of both genotype reduced their investigation time of the familiar female compared to the first trial, only *Dbh* +/− males spent more time investigating the novel female than the familiar female during the second trial (Fig. 5). When expressed as a preference score (time spent investigating the novel female minus time spent investigating the familiar female, divided by total investigation time), only *Dbh* +/− males showed a preference for the novel female (*Dbh* +/− 0.27 ± 0.04, *Dbh* −/− 0.02 ± 0.06, $P = 0.001$). No genotype differences were observed when only the familiar female was introduced during the second trial (data not shown). The social discrimination defect in *Dbh* −/− mice was also observed when females were used as both the test and stimulus animals (data not shown), indicating that changes in sexual behavior probably do not contribute to this phenotype. These results indicate that NA is not required for short-term social memory of a single stimulus animal, but is critical for distinguishing between familiar and novel animals.

3.3. Resident–intruder aggression

To determine whether NA contributes to territorial aggression, an intruder C57BL6/J male was placed into the home cage of singly housed *Dbh* +/− and *Dbh* −/− males over three trials spaced 2–3 days apart. We found that *Dbh* −/− mice nearly completely lacked an aggressive response. During the first trial, 6/13 resident *Dbh* +/− attacked the intruder at least once, and this ratio increased over trials (9/13 for trial 2, 11/13 for trial 3). In total, 12/13 *Dbh* +/− males attacked the intruder at least once over the three trials and most attacked the intruder during two or all three sessions. In contrast, only a single *Dbh* −/− male out of the 11 tested attacked an intruder during the entire testing period ($P < 0.0001$ by Fisher's exact test). Some resident *Dbh* −/− males displayed primarily defensive and submissive behaviors, while these behaviors were rarely, if ever, observed in resident *Dbh* +/− mice (data not shown). The one *Dbh* −/− male that displayed aggression attacked the intruder only during the third session, and did so for a very short time (∼2 s).

4. Discussion

We used *Dbh* −/− mice to assess the role of NA in various aspects of social behavior. To summarize the results, we

found that *Dbh* −/− mice have a normal response in three different anxiety tests, but are deficient in social discrimination and lack isolation-induced aggression. These results have implications for the contribution of NA to normal social behavior and social behavior deficits observed in various neurological and mood disorders.

4.1. NA and anxiety

NA is thought to play a central role in stress responses, including anxiety. Both the peripheral and central noradrenergic systems respond to stress by increasing activity and NA release. Because the locus coeruleus is activated under conditions of increased arousal and salience, this phenomenon appears to be an adaptive response to prepare the animal to react to potentially harmful environmental stimuli. However, chronic stress may cause hyperactivity of the NA response, leading to anxiety disorders [12]. For example, genetic ablation of α_{2A}-adrenoreceptors, which attenuates noradrenergic feedback inhibition via α_{2A} autoreceptor stimulation, increases anxiety in the elevated plus maze in mice [25]. Interactions between NA and neuropeptides such as CRF and galanin are also thought to contribute to stress responses [12,26]. Because increases in NA signaling can be associated with increases in anxiety, a decrease in NA signaling might be expected to decrease anxiety. For example, central administration of adrenergic antagonists or lesions of the locus coeruleus in rats reduced anxiogenic effects in the elevated plus maze [27,28]. We found no significant differences in anxiety-like behavior of *Dbh* −/− mice in the elevated plus maze, light/dark box, or open field test, although *Dbh* −/− mice tended to spend more time in the open arms of the elevated plus maze and took less time to re-enter the light side of the light/dark box. One explanation for the lack of a robust decrease in anxiety-like behavior in the knockouts is that *Dbh* −/− mice have reduced exploratory activity in novel environments. *Dbh* −/− mice have decreased locomotor activity in novel situations [29], and displayed fewer rears in the elevated plus maze and total crossings in the open field (this study). DSP-4 lesioned rats show a similar neophobic phenotype [30]. Another important point to consider is that, depending on the strain of animal used and the testing conditions, NA depletion can also increase or have no effect on anxiety [14]. Thus, while it appears that excessive NA signaling is usually anxiogenic, a lack of NA signaling is not necessarily anxiolytic.

4.2. NA and social memory

NA has been implicated in many types of learning and memory, including social memory. Attenuation of NA signaling via lesion or adrenergic antagonist causes pregnancy block in rats, and *Dbh* −/− mice lack parental behavior, two behaviors dependent on social memory [7,31,32]. We found that while *Dbh* −/− mice habituated and dishabituated investigatory behavior of a familiar or novel female, respectively, their ability to discriminate between a familiar and novel female presented simultaneously was impaired. In support of this result, the NA reuptake inhibitor nisoxetine enhanced social discrimination in rats, while rats with DSP-4 lesions of the locus coeruleus were unable to discriminate between novel and familiar animals [6,9]. The neuropeptides oxytocin and vasopressin are also critical for social memory in rodents [8,24,33]. In rats, oxytocin increases NA release in the olfactory bulb, and NA signaling appears to be required for oxytocin to modulate social memory. Strikingly, either neurotoxic depletion of NA or infusion of an α-adrenoreceptor antagonist in the olfactory bulb abolishes the preservation of social recognition by oxytocin [8,34]. Therefore, some forms of social memory depend on interactions between NA and neuropeptides. This may be of particular relevance to the loss of social recognition observed in Alzheimer's disease because of the profound loss of locus coeruleus NA neurons observed in post mortem Alzheimer's brains, which correlates with degree of dementia [35–37].

4.3. NA and aggression

The most robust and striking behavioral phenotype observed in this study was the nearly complete lack of aggressive behavior in *Dbh* −/− mice, suggesting that NA is required for resident–intruder/intermale aggression. In support of this hypothesis, NA is released during aggressive encounters [38,39], and aggression is enhanced by increases in NA signaling such as treatment with the NA reuptake inhibitor desipramine and in α_{2C}-adrenoreceptor knockout mice with impaired noradrenergic negative feedback control [17,19]. Conversely, NA depletion or β-adrenoreceptor blockade reduces isolation-induced aggression, although other forms of aggression can be enhanced [17,18]. In contrast with our results, a positive correlation was found between locus coeruleus cell loss and aggressive behavior in Alzheimer's disease patients [40]. One possible explanation is that adrenergic receptor supersensitivity caused by NA loss in Alzheimer's disease, and an excessive response to NA release may occur under some conditions. Our preliminary results suggest a hypersensitivity of central β-adrenergic receptors in *Dbh* −/− mice, but in contrast to the persistence of some NA and activation of adrenergic receptors in Alzheimer's disease patients, *Dbh* −/− mice have no ligand whatsoever and a complete absence of NA signaling, rendering the existence of hypersensitive receptors moot. We propose that the use of DBH inhibitors such as disulfiram to treat aggressive behavior warrants further investigation.

4.4. Clinical relevance

Although preclinical and clinical pharmacological findings have implicated NA in different types of social behavior, it has been difficult to define the clinical relevance of these findings. While a deficit in central NA is postulated to

contribute to cognitive disorders, it has yet to be confirmed as an underlying cause. In contrast, our results with the *Dbh* −/− mice have immediate clinical relevance because DBH enzymatic activity and *Dbh* genotype have been associated with disease. A common, single base polymorphism in the promoter region of the human *Dbh* gene (a C to T change at position—1021; T allele frequency ∼ 0.2) has been identified that controls serum DBH activity, probably by limiting *Dbh* transcription. Individuals with one "C" allele and one "T" allele at position—1021 (CT heterozygotes) have about half the DBH activity of CC homozygotes, while TT homozygotes have less than 10% CC activity [22]. Low DBH activity and/or presence of at least one low activity "T" *Dbh* allele have been linked to alterations in behavioral and disease states, including attention deficit and hyperactivity disorder [41–44], psychotic depression [45–47], cocaine-induced paranoia [48], autism [49,50], and Parkinson's disease [51]. Our results confirm and extend the involvement of DBH and NA in social behavior. This is especially important because many previous studies have used locus coeruleus lesions as a tool to understand NA function. One limitation of this approach is that because the entire neuron is ablated, co-expressed neuromodulators are removed in addition to NA, including ATP, neuropeptide Y, galanin, CART, and BDNF. In contrast, noradrenergic neurons and NA co-transmitters are intact in *Dbh* −/− mice ([52–54]; our unpublished data). Therefore, *Dbh* −/− mice may be a useful model for studying the relationship between DBH, NA, and specific symptoms of mood and behavioral disorders.

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