Effects of Maternal Stress on the Behavioral and HPA Responses of Offspring Exposed to the Predator or Non-Predator Odor in Brandt's Voles

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ABSTRACT

Maternal stress influences offspring survival strategies under predation risk. This study investigated foraging behavior and the hypothalamic-pituitary-adrenal (HPA) responses of Brandt's vole (*Lasiopodomys brandtii*) offspring after their mothers had been repeatedly exposed to predator odors during pregnancy. We exposed pregnant Brandt's voles to distilled water (DW, the control), rabbit odor (RO, non-predator odor), or cat odor (CO, predator odor) for 18 days (60 min/day). Once the offspring matured into adults, we exposed them to either rabbit odor or cat odor and recorded their behavioral and hormonal responses, as well as hypothalamic c-fos mRNA expression, were measured. Female CO offspring exposed to cat odor spent more time hiding and less time foraging, accompanied by the highest levels of serum adrenocorticotropic hormone (ACTH), serum corticosterone (CORT), and hypothalamic *c-fos* mRNA, compared to RO and DW offspring. When exposed to rabbit odor, male RO offspring showed more alerting behaviors than females, while male CO offspring showed more exploring behaviors than females. CO offspring exposed to rabbit odor exhibited higher levels of serum ACTH, serum CORT, and *c-fos* mRNA than those in RO and DW offspring. Our findings indicate that maternal stress induced by predator odor is sufficient to induce an altered HPA response, and these changes may be associated with increased hiding behaviors but decreased foraging behaviors in adult female offspring. Predator-induced maternal stress thus appears to be beneficial to increase the survival responses of vole offspring.

INTRODUCTION

To maximize fitness, animals must balance individual conditions, reproduction, and survival with environmental challenges, energy demands, and competition. Continued shaping by environmental forces may provide individuals with more variable advantageous phenotypes (Navarro-Castilla and Barja, 2019). Over evolutionary time, natural selection determines the prevalence of genotypes present in a population (Tian *et al*., 2021). Phenotypic plasticity allows individuals to adapt to environmental stress in a shorter period, however, and for parental experience to shape offspring phenotype via maternal effects (Wolf and Wade, 2009). Maternal effects are defined as the causal influence of the maternal genotype or phenotype on the offspring phenotype (Wolf and Wade, 2009). It is a phenotypic response of the offspring to environmental heterogeneity experienced by their mother during the perinatal period, which is not only affected by its genetic basis but also closely related to the experience and environment of its early life. Maternal effects play an important role in the regulation of small-mammal populations (Sheriff, 2015). If the maternal environment can predict what the offspring will experience, then maternal experiences during the perinatal period can influence the development of the offspring in ways that adapt them to the future environment, i.e., the "adaptive maternal effect" (Marshall and Uller, 2007). For

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example, offspring of the cichlid fish (*Neolamprologus pulcher*) adaptively develop faster escape responses and are more risk averse if their mothers had been exposed to predator cues during egg production (Sharda *et al*., 2021). Intrinsic state alterations induced by maternal density-induced stress lead to the maladaptive reproduction suppression in root voles (*Microtus oeconomus*) offspring and impair offspring capacity in response to the immediate environment (Bian *et al*., 2015).

Numerous studies have reported that animals exposed to predators or predator cues reduce foraging investment (Brown *et al*., 1988; Lima, 1998; Yin *et al*., 2011, 2017). A reduction in foraging investment may be beneficial for animals because it helps them reduce predation risk and thus improve their survival rate. The presence of predator cues increases prey alertness and reduces overall activity; because foraging in the presence of predators can be risky, prey must balance energy acquisition with safety. Risk-induced changes to foraging behavior can include increased vigilance, reduced foraging time, or foraging in safer areas that contain lower-quality food (Lima, 1998). Exposing pregnant mothers to predator odor can cause behavioral and physiological changes in prey offspring via gestational maternal effects (Bian *et al*., 2005; Murray *et al*., 2018). Pregnant mothers may transmit information about predators in the current environment to their offspring, resulting in a change in foraging strategies and survival rate for offspring under predation risk (Gingery *et al*., 2021). For example, when adult C57BL/6 mice are exposed to the same predator odor that their dams had been exposed to while pregnant, they decrease foraging but increase anxiety-like and anti-predator behaviors (St-Cyr and McGowan, 2015; St-Cyr *et al*., 2018). In addition, maternal exposure to predator odor had sex-specific effects on the hypothalamic-pituitary-adrenal (HPA) response in prey offspring (St-Cyr *et al*., 2017). Studies of maternal predator stress have been conducted using wild rodent species such as degus (*Octodon degus*) (Bauer *et al*., 2015) and tuco-tucos (*Ctenomys talarum*) (Brachetta *et al*., 2018). However, these studies did not use a non-predatory odor as a negative control to confirm that their findings are specific to predator odor stress.

Brandt's vole (*Lasiopodomys brandtii*) is an herbivorous rodent that inhabits the Baikal region of Russia, the Inner Mongolia part of China, and the eastern and central parts of the People's Republic of Mongolia (Zhang *et al*., 2003). The voles live in social groups, dig complex burrow systems, and reach population densities sufficient to damage grasslands (Zhong *et al*., 1985; Zhang *et al*., 2003). Understanding the factors that affect the behavior and physiology of Brandt's voles may help protect these grasslands. Previous studies have

reported that Brandt's voles responded readily to various stresses, such as hypoxia stress and social stress by the regulation of gene expression in the antioxidant defense system and OT/AVP system (Huang *et al*., 2021; Shi *et al*., 2022). Our previous study exposed voles to the odors of Siberian weasel (*Mustela sibirica*), cat (*Felis catus*), sunbeam snake (*Xenopeltis hainanensis*), goat (*Capra aegagrus*), and distilled water (control). Cat odor elicited the strongest defensive behavioral response and the greatest hypothalamic *c-fos* mRNA expression, which is an immediate-early gene (IEG) that can be rapidly initiated upon exposure to predator cues (Hegab *et al*., 2014b). Pregnant Brandt's voles exposed to cat urine odor produced more but lower-weight female offspring, while adult male offspring from dams exposed to cat odor showed more exploratory and foraging behaviors in a novel environment than the control (Gu *et al*., 2018, 2020). However, how vole offspring's foraging strategy change when they are exposed to the scent of the predator their mother had encountered is still unknown.

Here, we aimed to investigate how predator-induced maternal stress influences the foraging strategy of offspring exposed to predator odor. We exposed pregnant Brandt's voles to non-predator odor (rabbit urine odor) or predator odor (cat urine odor) and measured offspring foraging behaviors when exposed to the same two odors. We also want to elucidate the possible mechanisms of the HPA axis for this phenomenon. Our findings are expected to provide new ideas and basic information to help control rodent populations in Inner Mongolia. We hypothesized that adult Brandt's vole offspring of dams exposed to predator odor would show less foraging behaviors, accompanied by higher serum adrenocorticotropic hormone (ACTH), serum corticosterone (CORT), and hypothalamic *c-fos* mRNA levels, compared with the control. Moreover, one of our previous studies found that female offspring exposed to in utero predation risk displayed an enhanced level of estradiol which has been proved to increase the response of the HPA axis (Gu *et al*., 2020). Thus we predict that female offspring will be more sensitive to in-utero predation risk than males.

MATERIALS AND METHODS

Experimental animals

Wild Brandt's voles caught from the Inner Mongolian grasslands of China were housed in cages ($15 \times 22 \times 18$ cm) in male-female pairs at a controlled temperature of 21–23 °C, with a light/dark period of 12 h and the light period beginning at 07:00. Animals were fed *ad libitum* during the experimental period using a standard pellet diet (Yizheng Animal Biotechnology Co., LTD, Yangzhou, China) and distilled water. One hundred and eighty

3-month-old voles of similar weights were used, including 72 laboratory-bred first-generation individuals (Parents, 36 males and 36 females) and 72 second-generation individuals (F1 progeny, 36 males and 36 females).

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were approved by the Animal Care and Use Committee of Yangzhou University (No. SJXY-2).

Odor collection

The urine used in this study was obtained from an adult domestic male cat (*Felix catus*) and an adult male rabbit (*Oryctolagus cuniculus*). The cat was caught on the Wenhui Campus of Yangzhou University, China, while the rabbit was bought from a pet market in Yangzhou, China. The urine was collected by placing clean trays under the cages of the cat and rabbit. After 24 h, the collected urine was stored at -20 °C until the experiment started. The cat urine was used as a predator odor, and the rabbit urine was used as a non-predator odor, which is considered as a negative control, to indicate whether these findings are specific to predator odor stress or not.

Test apparatus

The test apparatus was prepared with opaque Plexiglas (75 × 37 × 40 cm). A 'hide box' was constructed from black Plexiglas to provide voles with cover. Food and odors were put on small plates and placed on two small circles (Gu *et al*., 2018). A camera (DS-2CC12C2T-IT5, Hikvision Digital Technology Co., Ltd., Hangzhou, China) connected to a computer was used to record animal behaviors.
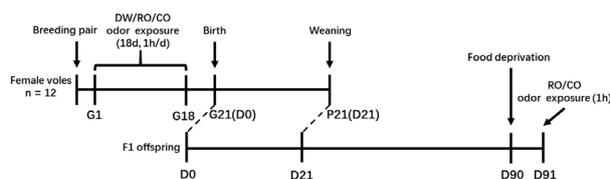

Fig. 1. Schematic illustration of the experimental design used in this study. All assayed adult F1 offspring experienced maternal treatment via their dams (in utero) exposure and an offspring treatment directly in the test apparatus. The sample size in each offspring treatment (RO/CO) of each maternal treatment (DW/RO/CO) was 12 per group (6M + 6F). DW, Distilled water; RO, Rabbit odor; CO, Cat odor; M, male offspring; F, female offspring; G, Gestation day; P, Postpartum day; D, Postnatal day.

Experimental procedures

Seventy-two laboratory-bred adult Brandt's voles (36

males and 36 females) were paired for breeding, and the vaginas of female voles were checked daily. The formation of a vaginal plug was considered as a sign of pregnancy, whereupon male voles were removed. Pregnant voles were randomly divided into three groups with 12 individuals per group: the cat odor group (CO), rabbit odor group (RO), and distilled water group (DW). The preserved cat and rabbit urines were defrosted and diluted using 5 units of water. Pregnant voles from the three groups were placed in the test apparatus and exposed to 10 mL diluted cat urine, 10 mL diluted rabbit urine, and distilled water, respectively, for 60 min. The apparatus was cleaned three times after each trial with cloth (distilled water, 75% ethyl alcohol, and distilled water, respectively). Between each exposure treatment, there was a 60-min interval. Within test days, the actual time of testing of each subject was randomized to prevent the development of time-based conditioning. These procedures were repeated for 18 consecutive days until parturition (Gestational period: 21 days) (Liu *et al*., 2013). This method for pregnancy identification was not entirely accurate, voles that did not give birth would be culled and alternative voles treated the same way would fill the vacancy.

Pups were housed together with their mothers until 21 days of weaning age (Liu *et al*., 2013), then removed and housed separately until 90 days of age. One male and one female offspring from each mother were then exposed at 9:00 AM to 10-mL-diluted samples of either rabbit urine or cat urine for 60 min in the test apparatus after 24-h of food deprivation (simulating a situation in which hungry voles forage in the presence of predator risk). The sample size in each offspring treatment of each maternal treatment was 12 per group (6M + 6F). Offspring behaviors were recorded during odor exposure (Fig. 1). After the 60-min odor exposure, offspring were immediately removed from the testing box and rapidly euthanized by decapitation, taking great care to avoid imposing stress on the voles. The blood was collected from the broken neck within 2 min. Hypothalamus tissues were collected from the brain using a Brain Matrix (Adult mouse, Sagittal, Stainless, RWD Life Science Co., Ltd., Shenzhen, China) and preserved in DNA/RNA protective solution (Takara Biotechnology Co., Ltd., Dalian, China). In this study, we focused on the offspring's responses to the same condition that their mothers had experienced, so we only recorded the offspring's behavioral video in the test apparatus, not including their mother's. As vole offspring were not born on the same day, the process of offspring odor-exposure treatments would last several days.

Behavioral responses

Offspring behavior during odor exposure in the test

apparatus was recorded by a digital video camera for 1h and scored later by an experimentally blind observer using Observer XT 7.0 software (Noldus Information Technology Co., Ltd., Wageningen, Netherlands). Six types of behaviors, referring to the method of Dielenberg and McGregor (2001), were configured in the Observer software. This method included the following behaviors: (1) hiding, the vole is completely hidden inside the hide box; (2) exploring, vole's nose going over the edge of the odor dish and sniffing the odor; (3) alerting, the vole is standing on its hind legs with forelegs retracted; (4) foraging, the vole is contacting food, including chewing or vibrissal sensing; (5) grooming, the vole is cleaning itself; (6) others, the vole is engaging in activities other than the five previously mentioned behaviors. Time spent in each behavior was manually quantified in seconds.

Hormonal responses

Serum was separated from blood using 3000×g centrifugation at 4°C for 30 min and then stored at -20 °C. Serum adrenocorticotropic hormone (ACTH) and corticosterone (CORT) levels were determined using an enzyme-linked immunosorbent assay kit for voles (Shanghai Jianglai industrial Limited by Share Ltd., Shanghai, China). ELISA tests of both ACTH and CORT were validated for Brandt's voles by Liu *et al.* (2020). The intra- and inter-assay coefficients of variation were < 9 and < 11%, respectively, for both ELISA kits. The assay range was 2.5–80 pg/L for ACTH and 15–480 μg/L for CORT. All samples were double diluted and assayed in duplicate. We plated 10 μL serum in a 96-well plate. The plate was washed five times using a 30-fold wash solution after incubation at 37 °C for 60 min. The horseradish-peroxidase conjugate reagent was then added to each well. After incubation at 37 °C for 60 min, the plate was washed five times and solutions A and B for chromogen were added. After 15 min incubation at 37 °C in the dark, a stop solution was added to stop the reactions. The optical density of each sample was determined at 450 nm using a Metertech microplate reader (BioTek Instruments Co., Ltd., Vermont, USA).

Total RNA extraction and quantitative real-time PCR amplification

Total RNA was extracted from the hypothalamus using a TRIZOL kit as described in the manufacturer's protocol of RNAiso Plus (Takara Biotechnology Co., Ltd., Dalian, China). RNAs were quantified using a spectrophotometer (NanoDrop Technologies Co., Ltd., Wilmington, USA). All samples with high-quality RNA (A260/A280 values > 1.8) were stored at -80 °C. Reverse transcription of RNA (1 μg) to cDNA was carried out following the Primescript RT reagent instructions using the gDNA Eraser (Takara

Biotechnology Co., Ltd., Dalian, China).

We used SYBR® green I-based quantitative real-time PCR to quantify the properties of the reverse transcription reactions, with three replicates per sample. The primers of *c-fos* (Forward primer: 5-TACGGAAACCGGAAACCCTCG-3; Reverse primer: 5-TGACTCCTTCCCTAGCTGGTC-3) and *β-actin* (Forward primer: 5-ATGCCAGAAGATTCCATACC-3; Reverse primer: 5-TTGTGCGTGACATCAAAGAG-3) for Brandt's voles were designed and verified by Hegab *et al.* (2014a). Each PCR reaction mixture (10 μL) contained 5 μL SYBR Premix EX Taq II, 1 μL cDNA, 0.4 μL of each gene-specific primer pair, 0.2 μL Rox reference Dye II, and 3 μL ddH$_2$O. The PCR was conducted in a real-time PCR system (Applied Biosystems 7500, Applied Biosystems, Inc., California, USA) using the following thermal cycling conditions: 95 °C for 30 s, followed by 40 cycles of 95 °C for 5 s, 60 °C for 34 s, and 72 °C for 30 s. The fold-change for gene expression was calculated using the relative quantification method ($2^{-\Delta\Delta Ct}$), with *β-actin* as the endogenous control. The average ΔCt for the control group was used to calibrate each sample.

Data analysis

Data were analyzed using SPSS 22.0 software, and the results were presented as mean±SEM (standard error of mean). Most behavioral data were not normally distributed, those data were analyzed using the non-parametric Kruskal-Wallis test, and the Mann-Whitney U test was determined the overall significant effects. Based on the assumptions of normality (Kolmogorov-Smirnov test) and homogeneity of variance (Levene's test), quantitative comparisons of three-way ANOVA (maternal treatment × offspring sex × offspring treatment) and two-way ANOVA (maternal treatment × offspring sex) among studied groups were performed for endocrine and gene expression data, followed by post-hoc pairwise comparisons with Bonferroni correction to reduce the false discovery rate from multiple comparisons. The output *P* values after Bonferroni correction are multiplied by the denominator 3 and then compared with α = 0.05. The independent-sample t-test was also used to analyze the differences between male and female offspring. Partial eta square (η^2_p), Eta square (η^2), Correlation Coefficient *r*, and Cohen's *d* were used as measures of the effect size. The level of significance at which the null hypothesis was rejected was α = 0.05.

RESULTS

Behavioral responses

    Offspring exposed to rabbit odor

Although we did not observe any significant

differences in behavioral responses of both male and female offspring exposed to rabbit odor among the three groups (Table I), we found that male CO offspring exhibited a longer duration of exploring behaviors (Z = -2.166, P = 0.026, r = 0.625, Fig. 2e) and other behaviors (Z = -2.082, P = 0.041, r = 0.601, Fig. 2f) than female CO offspring when they were exposed to rabbit urine odor. Male RO offspring exhibited longer duration of alerting behaviors than female RO offspring (Z = -2.023, P = 0.041, r = 0.584, Fig. 2b).

Offspring exposed to cat odor

We found significant differences both among male (x^2 = 9.310, P = 0.010, η^2 = 0.548) and female (x^2 = 6.351, P = 0.042, η^2 = 0.374) offspring exposed to cat urine odor from the three maternal treatment groups for the hiding behaviors (Table I). The Mann-Whitney U tests revealed that male CO offspring exhibited longer duration of hiding behaviors (Z = 2.882, P = 0.002, r = 0.832, Fig. 2a), but shorter duration of other behaviors than male RO offspring (Z = 2.722, P = 0.004, r = 0.786, Fig. 2f). Female CO offspring exhibited longer duration of hiding behaviors, but shorter duration of foraging behaviors than female DW offspring (Z = 2.402, P = 0.015, r = 0.693; Z = 2.882, P = 0.002, r = 0.832, respectively, Fig. 2a and c). Male CO offspring exhibited longer duration of exploring behaviors than female CO offspring (Z = 2.246, P = 0.026, r = 0.648, Fig. 2e). Female RO offspring exhibited longer duration of hiding behaviors (Z = 2.082, P = 0.041, r = 0.601, Fig. 2a),

but shorter duration of alerting and grooming behaviors than male RO offspring (Z = 2.246, P = 0.026, r = 0.648; Z = 2.246, P = 0.026, r = 0.648, respectively, Fig. 2b and d).
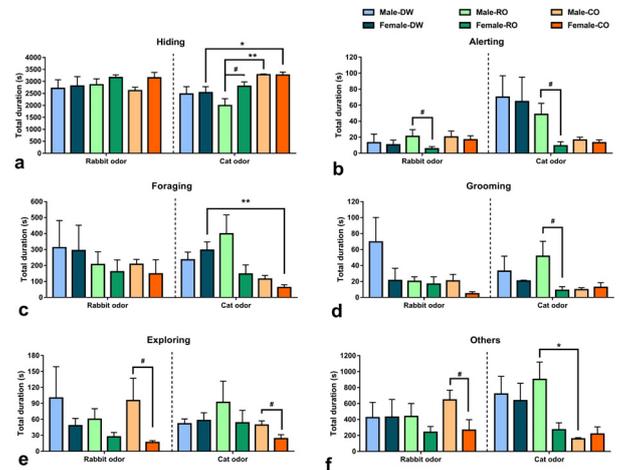

Fig. 2. Behavioral responses to acute rabbit odor or cat odor of offspring from dams exposed to distilled water (DW), chronic rabbit urine odor (RO), and chronic cat urine odor (CO) while pregnant (a: hiding; b: alerting; c: foraging; d: grooming; e: exploring; f: others). Data are mean±SEM. Significant differences among vole offspring from different maternal treatments are indicated as follows: *P < 0.05, **P < 0.01. Significant differences between male and female vole offspring are indicated as follows: #P < 0.05.

Table I. Effects of maternal treatment on behavioral responses of male and female offspring in Brandt's vole.

Offspring sex	Behavior	Offspring odor exposure									
		Rabbit odor					Cat odor				
		N	df	x^2	P	η^2	N	df	x^2	P	η^2
Male	Hiding	18	2	2.889	0.236	0.170	18	2	9.310	0.010*	0.548
	Alerting	18	2	2.961	0.228	0.174	18	2	4.118	0.128	0.242
	Foraging	18	2	0.456	0.796	0.027	18	2	4.538	0.103	0.267
	Grooming	18	2	2.689	0.261	0.158	18	2	4.275	0.118	0.251
	Exploring	18	2	0.817	0.664	0.048	18	2	0.105	0.949	0.006
	Others	18	2	2.351	0.309	0.138	18	2	7.871	0.020*	0.463
Female	Hiding	18	2	0.713	0.700	0.042	18	2	6.351	0.042*	0.374
	Alerting	18	2	3.075	0.215	0.181	18	2	5.406	0.067	0.318
	Foraging	18	2	0.713	0.700	0.042	18	2	8.561	0.014*	0.504
	Grooming	18	2	1.504	0.472	0.088	18	2	3.100	0.212	0.182
	Exploring	18	2	3.404	0.182	0.200	18	2	3.415	0.181	0.201
	Others	18	2	0.082	0.960	0.005	18	2	4.105	0.128	0.241

N, sample size; df, degrees of freedom; x^2, chi-squared; P, P value; *P < 0.05, η^2, Eta square.

Hormonal responses and hypothalamic c-fos mRNA expression

Three-way ANOVA showed that both maternal treatment and offspring treatment had significant main effects on serum ACTH, serum CORT, and hypothalamic *c-fos* mRNA levels of offspring (Table II). Offspring sex had a significant main effect on serum CORT level of offspring (Table II). There was no interaction effect among maternal treatment, offspring sex, and offspring treatment.

Table II. Results of three-way ANOVA on hormones and gene expression of Brandt's vole offspring.

Fixed factor/ Dependent variable	F	P	$\eta^2 p$
Maternal treatment			
ACTH	11.804	< 0.001***	0.282
CORT	38.091	< 0.001***	0.559
c-fos	12.23	< 0.001***	0.290
Offspring sex			
ACTH	0.163	0.688	0.003
CORT	7.638	0.008**	0.113
c-fos	0.451	0.504	0.007
Offspring treatment			
ACTH	6.317	0.015*	0.095
CORT	5.263	0.025*	0.081
c-fos	4.172	0.045*	0.065
Maternal treatment × Offspring sex			
ACTH	0.131	0.877	0.004
CORT	3.011	0.057	0.091
c-fos	0.674	0.513	0.022
Offspring sex × Offspring treatment			
ACTH	0.027	0.870	< 0.001
CORT	3.279	0.075	0.052
c-fos	0.523	0.473	0.009
Maternal treatment × Offspring treatment			
ACTH	0.697	0.502	0.023
CORT	0.663	0.519	0.022
c-fos	0.425	0.656	0.014
Maternal treatment × Offspring sex × Offspring sex			
ACTH	0.006	0.994	< 0.001
CORT	0.653	0.524	0.021
c-fos	0.491	0.615	0.016

ACTH, adrenalotropic hormone; CORT, corticosterone; *F*, F value; *P*, P value; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$, $\eta^2 p$, Partial eta square.

Hormonal responses of offspring exposed to rabbit odor

Two-way ANOVA showed significant main effects on serum ACTH ($F_{2, 30} = 24.540$, $P < 0.001$, $\eta^2 p =$ 0.621) and CORT ($F_{2, 30} = 7.638$, $P = 0.002$, $\eta^2 p = 0.337$) concentrations of offspring among the three groups when they were exposed to acute rabbit urine odor. Post hoc tests revealed that CO offspring had higher concentrations of serum ACTH than RO ($P < 0.001$, Cohen's $d = 2.331$) and DW offspring ($P < 0.001$, Cohen's $d = 2.557$, Fig. 3a), and CO offspring had the higher concentrations of serum CORT than RO offspring ($P = 0.002$, Cohen's $d = 1.544$, Fig. 3b). The concentration of serum CORT ($F_{1, 34} = 9.264$, $P = 0.005$, $\eta^2 p = 0.236$) was significantly different between male and female offspring. Male DW offspring had higher CORT concentration than females ($t = 2.562$, $P = 0.044$, Cohen's $d = 2.125$, Fig. 3b). The concentration of serum ACTH ($F_{1, 34} = 0.138$, $P = 0.712$, $\eta^2 p = 0.005$) was not significantly different between male and female offspring, and there were no significant interactions between maternal treatment and offspring sex (ACTH: $F_{1, 34} = 0.419$, $P = 0.662$, $\eta^2 p = 0.027$; CORT: $F_{1, 34} = 0.905$, $P = 0.415$, $\eta^2 p = 0.057$).
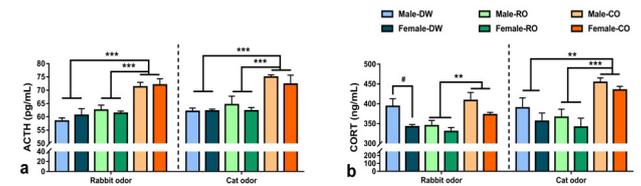
Fig. 3. Hormonal responses to acute rabbit odor or cat odor of vole offspring from dams exposed to distilled water (DW), chronic rabbit urine odor (RO), and chronic cat urine odor (CO) while pregnant (a: ACTH; b: CORT). Data are mean±SEM. Significant differences among vole offspring from different maternal treatments are indicated as follows: **$P < 0.01$, ***$P < 0.001$. Significant differences between male and female vole offspring are indicated as follows: #$P < 0.05$.

Hormonal responses of offspring exposed to cat odor

There were significant main effects on serum ACTH ($F_{2, 33} = 18.571$, $P < 0.001$, $\eta^2 p = 0.553$) and CORT ($F_{2, 33} = 12.562$, $P < 0.001$, $\eta^2 p = 0.456$) concentrations of offspring among the three groups when they were exposed to cat urine odor. Post hoc tests revealed that CO offspring had the higher concentrations of serum ACTH and CORT than RO ($P < 0.001$, Cohen's $d = 1.752$; $P < 0.001$, Cohen's $d = 2.219$, respectively, Fig. 3) and DW offspring ($P < 0.001$, Cohen's $d = 2.549$; $P = 0.002$, Cohen's $d = 1.629$, respectively, Fig. 3). The concentration of serum ACTH ($F_{1, 34} = 0.919$, $P = 0.345$, $\eta^2 p = 0.030$) and CORT ($F_{1, 34} = 2.786$, $P = 0.105$, $\eta^2 p = 0.085$) were not significantly different between male and female offspring, and there were no significant interactions between maternal treatment and offspring sex (ACTH: $F_{1, 34} = 0.277$, $P = 0.760$, $\eta^2 p =$

0.018; CORT: $F_{1, 34} = 0.073$, $P = 0.930$, $\eta^2 p = 0.005$).

Hypothalamic c-fos mRNA expression of offspring exposed to rabbit odor

c-fos mRNA expression in the hypothalamus of offspring exposed to rabbit urine odor was significantly different among the three groups ($F_{2, 33} = 11.701$, $P < 0.001$, $\eta^2 p = 0.438$, Fig. 4). CO offspring exhibited higher hypothalamic mRNA expression of *c-fos* than RO offspring ($P < 0.001$, Cohen's $d = 1.141$) and DW offspring ($P = 0.049$, Cohen's $d = 0.900$). *c-fos* mRNA expression was not significantly different between male and female offspring ($F_{1, 34} = 0.003$, $P = 0.960$, $\eta^2 p = 0.000$), and there was no significant interaction between maternal treatment and offspring sex ($F_{1, 34} = 0.093$, $P = 0.912$, $\eta^2 p = 0.006$).
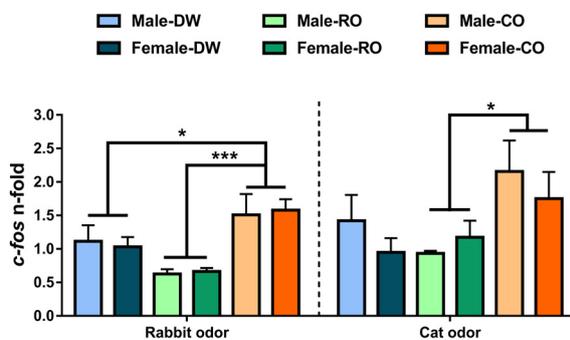

Fig. 4. Expression of *c-fos* mRNA of vole offspring exposed to acute rabbit odor or cat odor from dams exposed to distilled water (DW), chronic rabbit urine odor (RO), and chronic cat urine odor (CO) while pregnant. Data are mean±SEM. Significant differences among vole offspring from different maternal treatments are indicated as follows: *$P < 0.05$, ***$P < 0.001$.

Hypothalamic c-fos mRNA expression of offspring exposed to cat odor

c-fos mRNA expression in the hypothalamus of offspring exposed to cat urine odor was significantly different among the three groups ($F_{2, 33} = 4.543$, $P = 0.019$, $\eta^2 p = 0.232$, Fig. 4), with CO offspring showing higher hypothalamic mRNA expression of *c-fos* than RO offspring ($P = 0.027$, Cohen's $d = 1.143$). The expression of *c-fos* mRNA was not significantly different between male and female offspring ($F_{1, 34} = 0.648$, $P = 0.427$, $\eta^2 p = 0.021$), nor were there significant interactions between the maternal treatment and offspring sex ($F_{1, 34} = 0.483$, $P = 0.483$, $\eta^2 p = 0.047$).

DISCUSSION

This study investigated the effects of maternal exposure to predator odor on foraging behaviors and the HPA responses of offspring, using Brandt's voles as our study species. We found that offspring from dams exposed to predator odor during pregnancy exhibited less foraging behaviors, but more hiding behavior and stronger hormonal responses to the same predator odor, accompanied by a higher expression of *c-fos* mRNA in the hypothalamus, than offspring from dams exposed to non-predatory odor or distilled water during pregnancy.

After repeatedly exposing pregnant Brandt's voles to cat urine odor, even though their adult offspring had been starved for 24 h, both male and female CO offspring still exhibited a longer duration of hiding than the control when they were exposed to cat odor . In nature, upon recognizing a predator, prey may sacrifice foraging opportunities in favor of increased predator avoidance (Elvidge *et al*., 2014). Cat odor represents one of Brandt's vole's most feared predator odors (Hegab *et al*., 2014b). The adoption of such a foraging strategy by CO offspring in the present study that they spent more time hiding, meanwhile less time foraging and exploring when exposed to cat urine odor would probably reduce the possibility of being preyed on while a potential predator odor was nearby. Repeated exposure to predator odors represents a living environment with high predation risk. Dams exposed to predator odor might appear to pass this responsiveness to predator stress to their offspring via maternal effect, resulting in offspring exhibiting a more conservative foraging strategy under predation risk. Similar results have been documented in C57BL/6 mice that adult offspring of predator odor-exposed mothers showed increased avoiding behavior when they were exposed to predator odor (St-Cyr and McGowan, 2015).

The hypothalamus is the control center of the HPA axis that regulates visceral and endocrine activities (Pariante and Lightman, 2008). When prey is threatened by predators, the activation of the HPA axis causes prey to respond physiologically (Sapolsky, 2000; Herman *et al*., 2003). The hypothalamic paraventricular nucleus (PVN) secretes CRF and arginine vasopressin (AVP), which stimulates the secretion of ACTH in the anterior pituitary. In turn, the adrenal cortex is stimulated to secrete CORT. Increased CORT levels allow animals to mobilize more energy by inhibiting the absorption of sugar and increasing fat consumption from tissues. This energy release helps individuals resist the stress stimulus and respond to the stress (Sheriff and Thaler, 2014). In the present study, female vole offspring have a higher concentration of serum CORT than males. This phenomenon is common among mammals (Harris, 2020). Since the HPA axis is subject to gonadal influence (Viau, 2002). Estradiol increases but androgens decrease the HPA response to stressors,

thereby contributing to sex differences in HPA function. The sensitivity of the HPA axis to gonadal steroids is in part determined by exposure to gonadal hormones in early development (Green and McCormick, 2016). Compared to males, females have a greater stress-induced release of CRF, AVP, ACTH, and cortisol, which could be related to an increased sensitivity of their CRF receptors (Bangasser and Wiersielis, 2018), therefore, negative feedback is lower in females and this could result in further enhanced release of stress hormones by the adrenal cortex (Kokras *et al.*, 2019).

The present study showed that maternal exposure to different odors had a significant impact on offspring's HPA responses, while vole offspring have different HPA responses to rabbit and cat odors. So, we respectively investigated the HPA responses of offspring exposed to rabbit or cat odor. The concentrations of both ACTH and CORT in CO offspring were higher than those in RO and DW offspring, indicating that CO offspring were more sensitive to predation risk in the environment. The increased *c-fos* mRNA expression in the hypothalamus of CO offspring also showed the activation of hypothalamic neurons is elevated. The levels of adrenal CORT in the blood of wild animals change under chronic and acute predation stress (Newman *et al.*, 2013). Previous studies showed that the concentrations of ACTH and CORT in Norway rats and Brandt's voles are elevated, accompanied by higher defensive behavioral responses when they are exposed to cat odor compared to other predator and non-predatory odors (Yin *et al.*, 2011, 2017; Hegab *et al.*, 2014a, b). Short-term, rapid activation of the HPA axis can increase animals' survival-related behaviors and processes and is thus thought to be adaptive. Long-term or chronic activation of the HPA axis, however, has primarily been viewed as deleterious as prolonged CORT exposure can detrimentally affect reproduction, immune function, cognition, and metabolism in a variety of species (Harris, 2020; Lattin and Kelly, 2020). In the present study, adult offspring were exposed to acute predator odor, therefore, the results indicated that CO offspring exhibited a stronger behavioral and hormonal response to short-term predator odor exposure than RO and DW offspring. These offspring are more adaptive because they can quickly respond to predator odors. The result is also consistent with the prediction that predator-induced activation of the HPA axis inhibits foraging (Harris and Carr, 2016). There is some additional evidence in the literature that dams exposed to predator odor transmit stress information about predators to their offspring, thus enhancing the ability of their offspring to adapt to the environment (Almasi *et al.*, 2012; Ayers *et al.*, 2016).

When offspring from the three groups were exposed to rabbit odor, we did not observe any differences in the duration of any behaviors between the three groups and only obtained significant gender differences that male RO offspring spent more time alerting than female RO offspring. Male CO offspring spent more time exploring. However, the hormonal and *c-fos* mRNA levels of offspring exposed to rabbit odor were similar to those exposed to cat odor. Offspring from dams exposed to chronic cat odor that, in turn, were exposed to acute cat odor or rabbit odor showed the highest ACTH, CORT, and *c-fos* mRNA expression. Prenatal exposure to predator odor leads to sensitization of the HPA axis in Brandt's voles so that they have an elevated HPA activation whether they were exposed to the predator or non-predator odor. This hyperactivity is related to increased corticotrophin-releasing hormone signaling and impaired glucocorticoid receptor-mediated negative feedback (van Bodegom *et al.*, 2017). According to the match/mismatch theory, encountering prenatal stress prepares an organism for similar adversities during adulthood (Marshall and Uller, 2007), while a mismatching environment results in increased susceptibility to psychopathology (Nederhof and Schmidt, 2012). CO offspring with an elevated HPA activation can quick response to predator odor, but if CO offspring maintain an elevated HPA activation under non-predator odor exposure, they may consume unnecessary energy and have adverse effects. In this study, the offspring of Brandt's vole were only exposed to two odors, more attempts are needed to verify this conjecture in the future. Besides, we found that sex differences in behavioral responses were not consistent with hormonal and *c-fos* mRNA levels. This may be caused by the different locomotor activity of male and female voles, which are not entirely determined by HPA regulation. Higher levels of prey locomotor activity have been associated with a greater chance of being detected by predators and reducing activity is a widespread antipredator tactic (Lima, 1998). In the present study, female CO offspring exhibited a more conservative foraging strategy under predation risk may reduce the probability of being prey.

Prenatal stress in both animals and humans could result in long-term epigenome alterations which further lead to consequences for adaptation and development in the offspring (Kundakovic and Champagne, 2015). In the present study, 18-d odor exposure covered nearly the entire gestation period (21 d) of Brandt's voles (Liu *et al.*, 2013). Thus, the effects of predator odor stress on Brandt's vole offspring might be experienced indirectly in utero via prenatal epigenetic programming, and then, the functional growth of the HPA axis of offspring was impacted during embryonic development, with this effect on offspring continuing into adulthood. In addition, postpartum maternal

rearing behaviors can program offspring development and behavioral plasticity. Flexible rat maternal behavior shapes offspring development according to predator odor conditions (McLeod *et al*., 2007). Breast milk is the main source of nutrition for all newborn mammals, and changes in its composition are also a major factor in an individual's early-life development (Andreas *et al*., 2015). Moreover, recent studies on the gut-brain axis have implicated the microbiome in neurodevelopment and behavior. It is now widely accepted that maternal microbial transmission to offspring is universal across the animal kingdom (Funkhouser and Bordenstein, 2013). These studies indicate that there are multiple approaches affecting offspring phenotype via maternal stress. Mechanisms for behavioral and hormonal changes of offspring found in this study should be further explored.

CONCLUSION

Our results suggest that predator-induced maternal stress is sufficient to induce an altered hormonal HPA response, and these changes may be associated with increased hiding behaviors but decreased foraging behaviors in adult female offspring of Brandt's voles. Predator-induced maternal stress appears to be beneficial to increase the survival rate of offspring in voles because these offspring exhibit a more conservative foraging strategy under predation risk.

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IRB approval
All procedures performed in studies involving animals were approved by the Animal Care and Use Committee of Yangzhou University (No. SJXY-2).

Ethical statement
All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Statement of conflict of interest
The authors have declared no conflict of interest.

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