# Effects of Infertility by Cabergoline on Serum Sex Hormones and the Inter- and Intra-Sexual Social Behaviors of Female *Rattus losea*

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## ABSTRACT

Lesser rice-field rat is one of major pests in eastern and southern Asia, causing considerable losses in rice, vegetables, and other crops. The more serious situation was that *R. losea* has developed high resistance to anticoagulants with repeated and long-term application of anticoagulant rodenticides in southern China. Fertility control is considered as an alternative strategy for management of this pest. Cabergoline can inhibit prolactin (PRL) secretion and was applied in fertility control for animal, however, the physiological and behavioral mechanisms of cabergoline as a sterilant in practice remain little known. This study determined the effects of different doses of cabergoline on the inter- and intra-sexual social behavior and reproduction physiology in adult female lesser rice-field rats, *Rattus losea*. Results showed that the ovary weight of female rats treated with cabergoline significantly increased at day 24, but there were no notable changes in the uteri regardless dosage and time. PRL in female rats treated by 50 µg/kg cabergoline significantly was decreased by 56% at day 7 compared with the control. However, estradiol ($E_2$) in rats treated with 50 µg/kg cabergoline was higher than that in control group at day 24, and progesterone (P) secretion was not remarkably influenced by cabergoline. Moreover, the duration of investigation toward normal females in the 50 µg/kg groups at day 3 exceeded that of pre-treatment. The females treated by 100µg/kg cabergoline increased the frequency of investigation towards normal females and self-grooming and resting than pre-treatment. The duration of female investigation and defense towards normal males was lower in the 50-µg/kg groups at day 7 than the untreated group. Collectively, these data indicated that cabergoline might increase the amiable and sexual motivation behaviors of female *R. losea*, which implied that female rats sterilized by cabergoline still might keep the capacity of competitive reproductive interference.

## INTRODUCTION

Rodents remain among the world's most important pests (Munawar *et al*., 2018; Buckle and Smith, 2015; Prakash, 1988; Singleton *et al*., 1999), and are reservoirs for devastating human diseases (Brown *et al*., 2017). The lesser rice-field rat (*Rattus losea*) is such one of main nuisances, which causes considerable agricultural damage in eastern and southern Asia, mainly in southern China, Laos, Thailand, and Vietnam, and is an important reservoir of numerous pathogens, such as plague (Liu *et al*., 2010; Yang *et al*., 2006; Zhang and Wang, 1998). So far, *R. losea* still continues to bring about substantial losses to food crops such as rice, despite advances in methods of control and management techniques. In more serious cases, *R. losea* has developed high resistance to anticoagulants with

repeated and long-term application of anticoagulant rodenticides in south China (Wang *et al*., 2008). Thus, effective, safe, and sustainable pest control drug and methods that can control the growth of anticoagulant-resistant rodent populations should be developed.

The success of the pest rodent species can be attributed to their short lifespan, high rates of fecundity (high litter sizes, short gestation period and short duration to sexual maturity), potential to disperse long distances, complex social hierarchy, flexible social systems and their physiology and body structure which allow them to live in a wide range of environments (Buckle and Smith, 2015; Prakash, 1988). Traditional culling by baiting aims to increase the mortality rate of animal population and consequently decrease population numbers; however, it usually results in rapid population recovery as a result of the 'population bound effect' (Ericson, 1970), environmental contamination, and risks to non-target species (Zhang, 2000). As second-generation pest management strategy (Krebs, 2014), fertility control aims at reducing birth

rates of animal populations and overcoming the problems associated with traditional culling. Moreover, better control effect could be achieved by contraception than by simple culling when the 'competitive reproductive interference' is taken into account, since sterile individuals continue to draw on vital resources and could participate in mating competition (Caughley *et al.*, 1992; Chen *et al.*, 2017; Li *et al.*, 2019; Liu *et al.*, 2012; Liu *et al.*, 2013; Qin *et al.*, 2017; Shi *et al.*, 2002; Wang *et al.*, 2011; Zhang, 2000). In the light of complex social hierarchy and mating system of rodents, the behavioral mechanisms underlying competitive reproductive interference are very sophisticated and multifarious. However, whether the ability to attract heterosexual individuals of sterilized female or male is impaired or maintained remain little unknown. The extant knowledge gap in behavioral mechanisms currently limits our capacity to assess objectively and comprehensively the potential of sterilants, though the mechanism is critical for the effects of fertility control.

Cabergoline a dopamine agonist, can effectively suppress prolactin (PRL) secretion (Post *et al.*, 1988). Cabergoline has also been introduced to interfere with early gestational processes that require PRL in dogs (Jöchle *et al.*, 1989; Post *et al.*, 1988), cats (Jöchle *et al.*, 1989), rats (Ferraro *et al.*, 1995), foxes (Marks *et al.*, 2001), mouse (Su *et al.*, 2013, 2014), and other wild animals (Hearn *et al.*, 1998; Qin *et al.*, 2015a,b, 2017), and prevent females from lactating for a long period (Amenomori *et al.*, 1970; Bachelot and Binart, 2007; Ben-Jonathan *et al.*, 2008; Freeman *et al.*, 2000; Marks *et al.*, 2001; Mednick *et al.*, 1980). As a potential sterilant for pest rodents, cabergoline possesses certain advantages, including action in both sexes, low dosages, and long-lasting effect (Ferraro *et al.*, 1995; Qin *et al.*, 2015a,b, 2017; Su *et al.*, 2013, 2014). Nevertheless, the effects of cabergoline on social behaviors of animals and possibly on endocrine mechanism remain elusive.

In male *R. losea*, cabergoline reduces their serum luteinizing hormone, the sperm quality, and enzyme activity in testis (Qin *et al.*, 2015a,b), and decline times of aggression and investigation to normal male, but does not change times of investigation to normal female (Qin *et al.*, 2017). This implied that male *R. losea* sterilized with cabergoline still hold some opportunity to interfere reproduction of normal rats, since the mating system of *R. losea* isn't monogamy (Chen *et al.*, 2011). However, the effects of cabergoline on the physiology and behaviors in female *R. losea* remain unknown. To study the effect of cabergoline on physiology, we determined the variations of serum PRL, estradiol ($E_2$) and progesterone (P) levels in nonbreeding female *R. losea* under different doses and times. According to the mechanism of cabergoline

action, we predicted that serum PRL would decrease and $E_2$ secretion would increase to consequently reduce the number of dopamine receptors in treated females (Leong *et al.*, 1983). To analyze the effects of cabergoline on the social behaviours of females, we assigned dyadic encounters between treated female with normal male or female. PRL performs a significantly function in regulating the maternal behaviors of females (Freeman *et al.*, 2000). Previous studies clearly indicated that cabergoline suppresses PRL secretion. Thus, we infer that female *R. losea* would decrease amiable and sexual motivations behaviors.

## MATERIALS AND METHODS

### Animals and materials

Lesser rice-field rats (*Rattus losea*) used in all trials were trapped on a farmland in Zengcheng, Guangdong (23°18'N, 113°38'E) and then transported to Guangdong Institute of Applied Biological Resources. They were fed the rat pellets (Guangdong Medical Laboratory Animal Center, Guangzhou, China) and water *ad libitum*. Rats were housed individually in plastic cages (30 cm × 20 cm × 16 cm) and maintained in a cycle of 12 L:12 D (lights on from 08:00 to 20:00) at 24 ± 1 °C for 8 weeks prior to the behavior tests. All animal maintenance, trial protocols and sample collection protocols complied with the Institutional Animal Care and Use Committee of Guangdong Institute of Applied Biological Resources, Guangdong Academy of Sciences. Cabergoline (Tocris Bioscience, UK) was dissolved in sunflower oil at a dose of 50 and 100 μg/kg (body weight).

Forty adult females were divided randomly into five groups. There were no significant differences in body weight in five groups ($F_{4,35} = 0.464$, $P = 0.761$, mean body weight ± SE = 97.68 ± 2.76 g). Body weight had positive correlation with age of *R. losea*, by which female weight in 60-120 g was defined adult (Guo *et al.*, 2014). The control group (C) and four other treatment groups: C, 1.0 ml of oil for 3 consecutive days and tissue collection 24 days later; two groups treated by 50 μg/kg for 3 consecutive days and killed for tissue collection 7 and 24 days later; other two groups treated by 100 μg/kg for 3 consecutive days and killed for tissue collection 7 and 24 days later; which doses and time course were designed according some studies (Negishi and Koide, 1997; Marks *et al.*, 2001; Su *et al.*, 2013, 2014; Qin *et al.*, 2015a,b, 2017). After treatment, each group rats were fed normally. The female rats were weighed (±0.1 g) at 5 d intervals.

### Dyadic encounters

The dyadic encounter occurred in a glass box (length

× width × height = 80 cm × 40 cm × 80 cm). The box was surrounded by an opaque piece of chipboard to block the interference of each animal. The arena was partitioned into 2 equal compartments (40 cm × 40 cm × 80 cm) by removable cardboard (40 cm × 80 cm), and a rat from each pair was placed in one half of the arena. After a 5 min acclimatization period, the cardboard was removed, and the rats were allowed to interact for 30 min. Behaviors were recorded by digital video recorder. The arena was cleaned with water and 75% ethanol between trials (Liu et al., 2013).

Prior to cabergoline treatment, one female from the pre-treatment groups was assigned to dyadic encounters with one subject from the control group (C-female) on different days. Behaviors were observed for 30 min and videotaped. Forty adult males were assigned to a mating partner (mean body weight ± SE = 107.80±4.34 g, $F_{4,35}$ = 0.217, $P$ = 0.927, male weight in 60-150 g was defined adult (Guo et al., 2014). To 3 days after the encounter with a C-male, each rat encountered one normal male for 30 min. Females with similar body weights (within 10% difference) were paired up in two combinations in dyadic interactions. Females were treated with cabergoline for 3 days; one individual from post-treatment encountered the same individual from the C-female group on day 4 (1 day after the end of 3-day treatment) and day 21 (18 days after the end of 3-day treatment). Each group experiment was conducted at 3 d intervals.

The behavioral interactions were defined as follows: investigation, aggression, defense, amiable behavior, and self-oriented behavior (Cassaing and Isaac, 2007; Liu et al., 2013). The time and frequency of the above behaviors were recorded.

*Hormones and reproductive organs*

Female rats were sacrificed by decapitation between 09:00 and 11:00 h on 7 or 24 d after cabergoline treatment. Blood was collected and serum was separated from each blood sample by centrifugation at 4000g for 15min at 4°C, and stored at -80°C until hormone analysis. E₂, P and PRL were quantified by radioimmunoassay using $^{125}$I RIA kits (Beijing North Institute of Biological Technology, China). The inter- and intra-assay variations were less than 10% and 15%, respectively. The RIA kits were validated and used for a few wild rodent species following the standard kit instructions (Wang et al., 2006, 2011; Lv and Shi, 2011). Ovaries and uterus were dissected and weighed (±1 mg).

*Statistical analysis*

The two-way ANOVA was using to examine the effects of dosage and treatment time of cabergoline on serum hormone concentrations, body mass and organ weight. We performed least significant difference (LSD) test to compare the changes among the different groups, particularly between the females in the control group and the treatment group. Behavioral data were statistically analyzed by performing Mann-Whitney $U$ test or Wilcoxon signed-rank test to examine the differences between groups. $P < 0.05$ was considered significant. The data were presented as means ± SE. Results were analyzed using SPSS 13.0 for Windows.
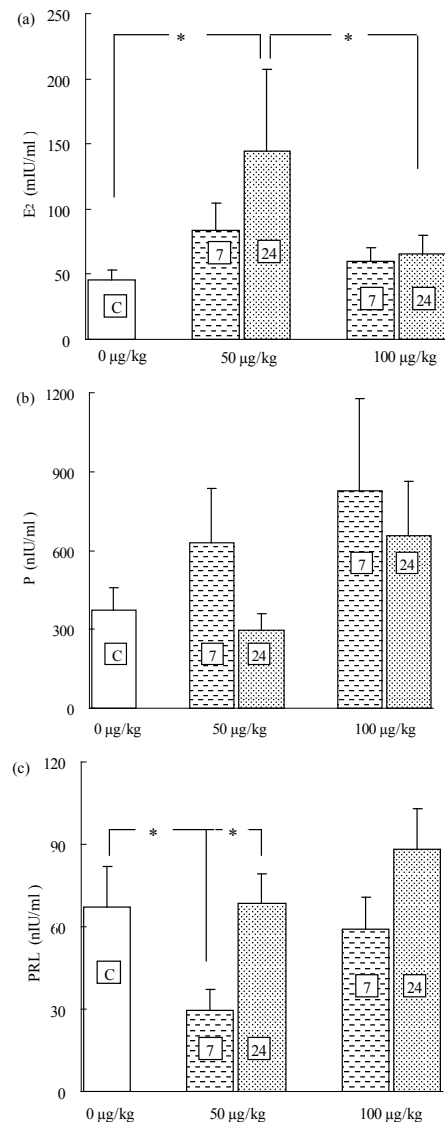


Fig. 1. Effects of cabergoline on serum concentrations of estradiol (a), progesterone (b) and PRL (c) in female lesser rice-field rats, *Rattus losea*. Mean (±SE) differences between groups were tested by LSD, * $P < 0.05$.

## RESULTS

*Sex hormones*

There were no significant effects of drug dosage ($F_{2,34}$ = 1.641, $P$ = 0.209) and time course ($F_{2,34}$ = 2.571, $P$ = 0.091) on the $E_2$ content. However, the $E_2$ concentrations in female lesser rice-field rats treated with 50 µg/kg cabergoline increased by more than three times at day 24 compared with those in the control group ($P$ = 0.020, Fig. 1a). Drug dosage and time course did not affect P level (D: $F_{2,32}$ = 1.041, $P$ = 0.365; T: $F_{2,32}$ = 1.183, $P$ = 0.319), and there were no differences between all groups (Fig. 1b). Time course ($F_{2,31}$ = 3.641, $P$ = 0.038), not cabergoline dosage ($F_{2,31}$ = 1.961, $P$ = 0.158), significantly affected PRL concentration. At 50 µg/kg cabergoline, PRL concentrations decreased significantly by 56% at 7 d compared with those in the control group ($P$ = 0.037) and recovered at day 24 ($P$ = 0.037, Fig. 1c).

*Body weight and reproductive organs*

The results showed that 50 or 100 µg/kg cabergoline did not change the body weight of females during the entire experiment ($P$ > 0.05). The drug dosage and time course did not affect the wet weight of the ovary (D: $F_{2,35}$ = 3.262, $P$ = 0.050; T: $F_{2,35}$ = 1.424, $P$ = 0.254) and uterus (D: $F_{2,35}$ = 2.017, $P$ = 0.148; T: $F_{2,35}$ = 0.697, $P$ = 0.505). The ovary of the female rats treated with 50 µg/kg cabergoline

at 24 d increased in comparison with those of the control females ($P$ = 0.017 and exceeded those of the rats treated with 100 µg/kg cabergoline at 24 d ($P$ = 0.036, Fig. 2a).

*Behavioral interactions in varied groups*

Cabergoline also affected the social behaviors of female *R. losea*. The duration of individual investigation toward normal females was more than two times longer in the 50 µg/kg group compared with that in pretreated group at day 4 after treatment ($Z$ = −2.380, $P$ = 0.017, Table I), whereas the duration of self-grooming and resting simultaneously decreased by 14.5% ($Z$ = −2.240, $P$ = 0.025, Table I). The frequency of self-grooming and resting ($Z$ = −2.173, $P$ = 0.030; $Z$ = −2.028, $P$ = 0.043, Table I) and investigation ($Z$ = −2.313, $P$ = 0.021; $Z$ = −1.973, $P$ = 0.049, Table I) toward normal females increased significantly in the 50 and 100 µg/kg groups compared with the pretreated groups at day 4 after treatment.

The dyadic encounter with normal males, the duration of individual female investigation ($Z$ = −2.313, $P$ = 0.021) and defense were evidently lower in the 50 µg/kg group at day 7 compared with pretreated groups ($Z$ = −2.366, $P$ = 0.018, Table II), whereas the duration of self-grooming and resting decreased by 12.19% ($Z$ = −2.521, $P$ = 0.012, Table II). The frequency of investigative behaviors toward males decreased in females treated with 50 and 100 µg/kg cabergoline at day 7 ($Z$ = −2.524, $P$ = 0.012; $Z$ = −2.383,

**Table I. Comparison of females' investigation, aggression, defense and self-grooming and resting times (T, sec) and frequency (F) in 30 min encounters with control females between the control and the treated females.**

| Dose (µg/kg) | Treated female toward control | | Investigation | Aggression | Defense | Self-grooming and resting |
|---|---|---|---|---|---|---|
| 50 | Pre-treat | T | 165.1 ± 37.7B | 9.0 ± 9.0 | 15.0 ± 15.0 | 1610.9 ± 45.4A |
| | | F | 9.8 ± 1.5b | 0.4 ± 0.4 | 0.5 ± 0.5 | 10.8 ± 1.5b |
| | Post-treat day 4 | T | 366.9 ± 59.6A | 0.0 ± 0.0 | 28.9 ± 19.5 | 1376.6 ± 87.1B |
| | | F | 22.5 ± 3.1a | 0.0 ± 0.0 | 0.3 ± 0.2 | 23.5 ± 3.4a |
| | Post-treat day 21 | T | 181.0 ± 42.6B | 0.0 ± 0.0 | 0.0 ± 0.0 | 1610.4 ± 47.3A |
| | | F | 11.4 ± 1.4b | 0.0 ± | 0.0 ± 0.0 | 11.9 ± 1.5b |
| 100 | Pre-treat | T | 168.8 ± 42.7 | 15.0 ± 15.0 | 9.0 ± 9.0 | 1607.3 ± 48.2 |
| | | F | 9.0 ± 2.4b | 0.5 ± 0.5 | 0.4 ± 0.4 | 9.8 ± 2.3b |
| | Post-treat day 4 | T | 214.8 ± 30.6 | 0.0 ± 0.0 | 32.5 ± 32.5 | 1552.8 ± 19.2 |
| | | F | 16.4 ± 2.2b | 0.0 ± 0.0 | 0.8 ± 0.8 | 17.5 ± 2.0a |
| | Post-treat day 21 | T | 256.9 ± 70.6 | 16.4 ± 16.4 | 0.0 ± 0.0 | 1526.8 ± 82.1 |
| | | F | 13.5 ± 2.3b | 0.6 ± 0.6 | 0.0 ± 0.0 | 13.8 ± 2.3a |

Note: Prior to cabergoline treatment (pre-treatment), one female subject from the pretreated groups was assigned to dyadic encounters with one subject from the control group (C) on different days. Females were treated with cabergoline for 3 days (post-treatment); one individual encountered the same individual from the C group on day 4 and on day 21 respectively. Data are the mean±s.e.m. Means with different superscript letters vary significantly at $P$ < 0.05 by the Wilcoxon signed-rank test.

**Table II. Comparison of females' investigation, aggression, defense and self-grooming and resting times (T, sec) and frequency (F) in 30 min encounters with a male counterpart between the pre-treatment and the post-treatment.**

| Behavioral interactions | | 50 µg/kg (pre- and post- treated female toward normal male) | | | |
|---|---|---|---|---|---|
| | | Pre-treated | Post- treated day 7 | Pre-treated | Post- treated day 24 |
| Investigation | T | 184.8 ± 43.4 | 86.9 ± 24.2* | 234.6 ± 45.7 | 183.0 ± 73.0 |
| | F | 20.0 ± 3.4 | 7.6 ± 1.8* | 16.8 ± 2.2 | 14.6 ± 3.2 |
| Aggression | T | 18.8 ± 13.8 | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 |
| | F | 0.6 ± 0.3 | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 |
| Defense | T | 66.6 ± 18.7 | 0.0 ± 0.0* | 120.8 ± 64.5 | 23.4 ± 13.4* |
| | F | 8.4 ± 3.8 | 0.0 ± 0.0* | 1.9 ± 0.8 | 1.0 ± 0.6 |
| Self-grooming and resting | T | 1527.0 ± 33.8 | 1713.1 ± 24.2* | 1444.6 ± 104.0 | 1593.6 ± 82.5 |
| | F | 23.6 ± 2.8 | 7.9 ± 1.8* | 18.5 ± 2.4 | 16.1 ± 3.7 |

Note: Prior to cabergoline treatment (pre-treatment), each female rat encountered one normal male for 30 min. Then females were treated with 50 µg/kg cabergoline for 3 days (post-treatment); one individual from post-treatment encountered the same normal male on day 7 and on day 24 respectively. Data are the mean±s.e.m. Differences between the pre-and the post-treatment group were tested using the Wilcoxon signed-rank test, * $P < 0.05$.

**Table III. Comparison of females' investigation, aggression, defense and self-grooming and resting times ( , sec) and frequency (F) in 30 min encounters with a male counterpart between the pre-treatment and the post-treatment.**

| Behavioral interactions | | 100 µg/kg (pre- and post- treated female toward normal male) | | | |
|---|---|---|---|---|---|
| | | Pre-treated | Post- treated day 7 | Pre-treated | Post- treated day 24 |
| Investigation | T | 251.0 ± 58.7 | 178.5 ± 32.3 | 242.6 ± 43.3 | 196.7 ± 68.1 |
| | F | 19.6 ± 4.0 | 10.4 ± 1.6* | 22.7 ± 3.3 | 14.6 ± 2.4 |
| Aggression | T | 0.6 ± 0.6 | 0.0 ± 0.0 | 60.1 ± 52.6 | 0.0 ± 0.0* |
| | F | 0.1 ± 0.1 | 0.0 ± 0.0 | 2.7 ± 2.4 | 0.0 ± 0.0* |
| Defense | T | 21.0 ± 21.0 | 25.3 ± 25.3 | 4.7 ± 2.5 | 0.0 ± 0.0 |
| | F | 1.3 ± 1.3 | 1.0 ± 1.0 | 0.7 ± 0.4 | 0.0 ± 0.0 |
| Self-grooming and resting | T | 1527.4 ± 48.6 | 1596.3 ± 46.8 | 1478.6 ± 80.5 | 1603.3 ± 68.1 |
| | F | 21.8 ± 3.2 | 11.6 ± 1.4* | 25.9 ± 3.2 | 15.1 ± 2.5* |

Note: Prior to cabergoline treatment (pre-treatment), each female rat encountered one normal male for 30 min. Then females were treated with 100 µg/kg cabergoline for 3 days (post-treatment), one individual from post-treatment encountered the same normal male on day 7 and on day 24 respectively. Data are the mean±s.e.m. Differences between the pre-and the post-treatment group were tested using the Wilcoxon signed-rank test, * $P < 0.05$.

$P = 0.017$, TableII and III). The frequency of defense toward males in the 50 µg/kg group at day 7 were lower than that in the pretreated group ($Z = -2.366$, $P = 0.018$, Table II). The frequency of self-grooming and resting decreased in treatment groups ($P < 0.05$, Table II and III), except for the 50 µg/kg group at day 24 ($P > 0.05$, Table II and III).

## DISCUSSION

Our data showed that the PRL in female *R. losea* decreased in response to the 50 µg/kg cabergoline treatment at day 7 and that 50 µg/kg cabergoline treatment raised $E_2$ secretion at day 24, which agreed with our prediction. This could be because $E_2$ controls PRL gene expression, regulates its sensitivity, and inhibits PRL (Freeman *et al*., 2000; Lieberman *et al*., 1981; Maurer, 1982). As previously reported, $E_2$ is antidopaminergic at the lactotroph, and its secretion increases to decrease the number of dopamine receptors (Leong *et al*., 1983). Thus, PRL may be released subsequently in response to dopamine receptors decreases at day 24. No direct evidence is currently available to determine whether P is an autocrine or paracrine to regulate PRL secretion (Freeman *et al*., 2000). In this study, P secretion of female *R. losea* was not influenced by 50 or 100µg/kg cabergoline. Moreover, we

did not find the correlation between P and PRL in female *R. losea*. Our data indicated that the serum $E_2$, P, and PRL of females treated with 100 µg/kg cabergoline were not significantly different compared with those of the control group. In general, the effects of cabergoline suppression on PRL, which is influenced by the dosage and the usage of excessively high concentration of cabergoline in a short time, may cause rapid changes in the neuroendocrine system facing challenge, pressure, hormone and/or neurotransmitter and their receptors in target organ in female *R. losea*. In addition, under various delivery modes and different species, the bioavailability of cabergoline was different, 30% in mice and 63% in rats (Leong *et al.*, 1983). Therefore, further studies should be conducted that determine the appropriate dosage of cabergoline in various rodent species.
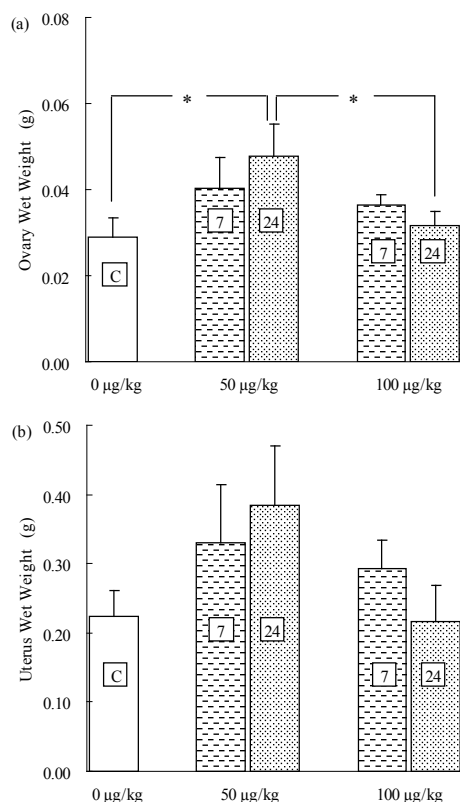


Fig. 2. Effects of cabergoline on the wet weight of ovary (a) and uterus (b) of female *Rattus losea*. Mean (±SE) differences between groups were tested by LSD, * $P < 0.05$.

Our study indicated that the ovary weight of female rats treated with 50 µg/kg cabergoline at day 24 were significantly increased by 64.6% compared with those in the control group, and increased by 52.1% more than those of rats treated with 100 µg/kg cabergoline at day 24. A significant change in ovary weight may be attributed to cabergoline causing the variation of serum PRL. The neural circuitry regulating of PRL is particularly sensitive to ovarian steroids. Therefore, cell growth, migration, and differentiation in tissues are finally influenced (Beitrame *et al.*, 1996; Freeman *et al.*, 2000). Most uteruses of female treated with cabergoline showed that edema because the dopaminergic neurons express $E_2$ and/or P receptors. This result is possibly induced by the regulation of Angiotensin II (ANG II) receptors (Kohama *et al.*, 1992; Nagano and Kelly, 1994). ANG II is important in regulating blood pressure, vascular tone, and salt and water homeostasis (Warembourg *et al.*, 1989). If this factor is one cause of the resulting uterine edema in female *R. losea* under cabergoline treatment, the question deserves further study. In the field, the social behaviours of a target animal may reflect its capacity for resource acquisition and social status (Benus *et al.*, 1991; Bottari *et al.*, 1993). Active investigative behavior between intrasexual individuals may state the social status of animals (Chen *et al.*, 2011; Chen *et al.* 2017; Liu *et al.* 2013; Negishi and Koide, 1997; Qin *et al.*, 2017; Wang *et al.* 2011). The investigation time and frequency of female *R. losea* toward normal females after 50 µg/kg cabergoline treatment were higher compared with that in the pretreated group, particularly in the group at day 4 after treatment. The duration of self-grooming and resting of female treated by 50 µg/kg cabergoline toward normal female decreased significantly compared with that of the pretreated group at day 4, whereas the frequency of self-grooming and resting increased within the same period. These results implied that cabergoline changed the females' social status and tensity after treatment. However, the effect of cabergoline on the investigative behavior of female toward normal female was not observed at day 21 after treatment, which indicated the effect of cabergoline was restorable as time goes on.

Investigative behavior between intersexual individuals mainly represents amiable and sexual motivations (Cassaing and Isaac, 2007; de Boer *et al.*, 2003). The duration and frequency of female *R. losea* investigation towards untreated adult males was lower in the 50 µg/kg group at day 4 compared with the untreated group. Therefore, 50 µg/kg cabergoline may change the relationship between male and female rats. Aggressive behavior in intersexual or intrasexual conspecific individuals plays an important role in social status, resources, and defense of territory throughout biology (Benus *et al.*, 1991; Bottari *et al.* 1993; Liu *et al.*, 2012; Liu *et al.*, 2013; Wang *et al.* 2011). Our data showed that aggression in cabergoline-treated female *R. losea* is lesser than that in nontreated females and the defense behavior exhibits a similar trend. Cabergoline

reduces the aggression of female *R. losea* toward adult males and generally may reflect that females promote amiable will and sexual motivations toward adult male.

The regulatory mechanism that cabergoline may induce the change of behavior in females was still unclear. This result is apparently regulated through the PRL and/or $E_2$ cycle. PRL performs a significantly function in regulating the maternal behaviors of females, including cleaning, gathering, grouping, and nursing of the young (Freeman *et al*., 2000). Previous studies clearly indicated that the dopamine agonist bromocriptine suppresses PRL secretion and prevents the onset of maternal behavior (Spritzer *et al*., 2005). Moreover, $E_2$ participates in sexual solicitation to males in mammals (Raymond *et al*., 1978). Thus, we infer that increase in amiable and sexual motivation behaviors in female *R. losea* may be attributed to $E_2$ secretion caused by cabergoline.

## CONCLUSION

Cabergoline does not weaken those social behaviors between intra- and inter-sexuality in female *R. losea*. These females still are able to keep competitive in holding vital resources and mates compared with normal females, which will contribute more effect in fertility control. Collectively, cabergoline is a potentially effective sterilant for pest rodent. Further efforts should be made to reduce costs of cabergoline bait, and explore the optimal strategy of field practice in pest rodent control.

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*Statement of conflict of interest*
The authors declare that there is no conflict of interests regarding the publication of this article.

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