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Cabergoline Reduces Serum Luteinizing Hormone and Sperm Quality in Male *Rattus losea*

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Abstract.- Studies have rarely focused on the effect of cabergoline dosage and duration on normal male animal and human. We examined the serum concentrations of four hormones, reproductive organ weight, and sperm quality of adult male lesser rice-field rats (*Rattus losea*) after cabergoline treatment. Forty male rats were randomly divided into five groups and treated with cabergoline given by gavage daily for 3 d at three doses (0, 50, and 100 μg/kg). Animals were euthanized at 7 and 24 days after the end of treatment. Results showed that cabergoline did not affect follicle-stimulating hormone levels. Compared with control, testosterone concentrations decreased significantly by 48.6% at 7 d after treatment with 100 μg/kg cabergoline. Luteinizing hormone concentrations were significantly reduced by cabergoline dosage and time course. Time course affected sperm density and sperm deformity rate. Cabergoline dosage and time course significantly affected male sperm vitality at 50 μg/kg. Moreover, cabergoline significantly decreased the percentage of 'rapid', 'slow or sluggish' progressive motility sperms, and increased the percentage of "immotility" sperms. The present study suggests that cabergoline may reduce luteinizing hormone level, and impair sperm quality, which hint weakening reproductive effects on male *R. losea*.

Key words*:* Cabergoline, prolactin, *Rattus losea*, sperm quality.

INTRODUCTION

Prolactin (PRL) is important for the reproduction of female mammals. As a PRL-inhibiting factor agonist, cabergoline can interfere with reproductive processes that require PRL, induce abortion in pregnant animals, and prevent females from lactating for a long period (Amenomori *et al.*, 1970; Mednick *et al.*, 1980; Ferraro *et al.*, 1995; Freeman *et al.*, 2000; Bachelot and Binart, 2007; Ben-Jonathan *et al.*, 2008; Egli *et al.*, 2010). Thus far, cabergoline has been applied to control the fertility of some nuisance or damaging female animals, including feral female cats (Jöchle and Jöchle 1993), fox (*Vulpes vulpes*) (Marks *et al.*, 1996, 2001, 2002), stoat (*Mustela erminea*) (Norbury, 2000), rat (Ferraro *et al.*, 1995; Negishi and Koide, 1997), and mouse (Su *et al.*, 2013, 2014). In contrast to studies on female animals, studies have rarely revealed the effects of cabergoline on male reproduction and the underlying mechanisms of such effects.

Previous sporadic and indirect studies suggested that cabergoline can suppress PRL secretion and change the levels of other reproductive hormones in males (Rao *et al.*, 1984; Oseko *et al.*, 1991; De Rose *et al.*, 1998, 2003; Koch *et al.*, 2006). Bromocriptine, another dopamine agonist that suppresses PRL secretion, increases the plasma levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in male rats; likewise, this dopamine agonist increases the plasma levels of FSH, LH, and testosterone in male mice at higher doses than that used in rats (Rao *et al.*, 1984). However, the use of bromocriptine for more than two weeks can reduce testosterone plasma levels in normal human males (Oseko *et al.*, 1991). Moreover, the biological functions of a dopamine agonist depend on species, age, hormonal status, dosage, and treatment period. Cabergoline may affect the suprabasal secretion of PRL and suppresses the pulse frequency of testosterone in male dogs (Hess, 2006; Koch *et al.*, 2006). In male patients with

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hyperprolactinemia, cabergoline treatment can normalize serum PRL levels and restore libido as well as the number and quality of sperms (De Rose *et al.*, 1998, 2003). Cabergoline substantially increases the possibility of sustaining multiple orgasms in rapid succession during sex in normal human males and have no side effects (Krüger *et al.*, 2003; Egli *et al.*, 2010). This raises an intriguing possibility that cabergoline through PRL signaling mediated actions of the male reproductive system, its hormonal regulation, or hypothalamic centers that control sexual behavior.

Lesser rice-field rat (*Rattus losea*), as the dominant rodent species in farmland in eastern and southern Asia, causes considerable agricultural damage and is an important reservoir of many causative agents, such as plague. Moreover, its ecological habit, growth, population dynamics, hazard has also been studied (Zhang and Wang, 1998; Liu *et al.*, 2010; Chen *et al.*, 2011). The rodent control should be a general management much more than the simple and single poisoning practice (Rustamani *et al.*, 2005). With repeated and long-term application of anticoagulant rodenticides in the Guangdong region, *R. losea* has developed high resistance to first-generation anticoagulants with the resistance rate ranges from 16.7% to 36.7% (Wang *et al.*, 2008). Therefore, fertility control becomes an alternative strategy for effective, safe, and sustainable control of pest rodents who have developed anticoagulant- resistance (Fu *et al.*, 2013; Liu *et al.*, 2013; Krebs, 2014). Moreover, *R. losea* breeds the whole year in Guangdong (Zhang and Wang 1998) and its mating system is not monogamy (Chen *et al.*, 2011). Therefore, a sterilant such as cabergoline will be more suited for fertility control of both sexes of *R. losea* (Su *et al.*, 2014). Although PRL exhibits pleiotropic functions in immunization, osmoregulation, and reproduction (Ben-Jonathan *et al.*, 2008; Egli *et al.*, 2010), and cabergoline can decrease PRL in some abnormal male animals and human, however, systematic knowledge is still limited regarding the effects of cabergoline on the physiology of normal male. The present study is aimed at systematically examining the effects of cabergoline on hormones, reproductive organs and sperm of male *R. losea* under captive conditions.

MATERIALS AND METHODS

Animals and treatment

All lesser rice-field rats (*Rattus losea*) used in this study were live-trapped on a farmland in Feng Village (23°18'N, 113°38'E) in Zengcheng, Guangdong in September 2011 and then transported to Guangdong Entomological Institute. Adult rats were housed individually in plastic cages (30 cm × 20 cm × 16 cm) with food (rat pellets produced by Guangdong Medical Laboratory Animal Center) and water *ad libitum*. These cages were maintained 12 L:12 D (with lights on from 08:00 to 20:00) at 25±1°C for 8 weeks prior to the behavior tests. All animal housing, care, and procedures complied with the Institutional Animal Care and Use Committee of Guangdong Entomological Institute, Guangdong Academy of Sciences.

Forty adult males were divided randomly into five groups (8 rats in every group, mean body weight ± SE = 107.80 ± 4.34 g, $F_{4,35}$ = 0.217, P = 0.927, body weight had positive correlation with age of *R. losea*, Male weight in 60-150 g was defined adult. Guo *et al.* (2014): the control group (C) and four other treatment groups: two groups treated with 50 μg/kg cabergoline for 3 consecutive days and sacrificed for tissue collection 7 and 24 days later, respectively; other two groups treated with 100 μg/kg cabergoline for 3 consecutive days and sacrificed for tissue collection 7 and 24 days later, respectively. The doses and time course followed similar studies done in other laboratories (Ferraro *et al.*, 1995; Negishi and Koide, 1997; Su *et al.*, 2013, 2014). Cabergoline (Tocris Bioscience, UK) was dissolved in peanut oil, 1.0 ml solution was given to male rats by gavage, and control rats (C) were treated with only 1.0 ml of peanut oil for 3 days, and sacrificed for tissue collection 24 days later. After treatment, the rats in each group were fed normally. The male rats were weighed (±0.1 g) every 5 days.

Hormones, reproductive organs and sperm

After 7 or 24 days of cabergoline treatment, male rats were anesthetized with ether, and then sacrificed immediately by decapitation between 09:00 h and 11:00 h. Trunk blood was collected and serum was separated from each blood sample by centrifugation at 1000×g for 20 min at 4°C and stored at -80°C until

hormone analysis. FSH, LH, PRL and testosterone were quantified by radioimmunoassay using ^{125}I RIA kits (Beijing North Institute of Biological Technology). These RIA kit were validated and used for few wild rodent species following the standard kit instructions (Wang *et al.*, 2006, 2011; Lv and Shi, 2011). The inter- and intra-assay variations were less than 10% and 15%, respectively.

Testes, epididymides, and seminal vesicles were dissected and weighed (±1 mg) (Hijazi *et al.*, 2012). We removed one side of the epididymis and opened the cauda up with a pair of scissors in 0.9% normal saline (37°C) to configure as 10% sperm solution. Seminal parameters were defined as follows (World Health Organization, 1999): Sperm density was measured by hemacytometer count at ×200 magnification. Sperm motility was graded as follows: a, rapid progressive motility; b, slow or sluggish progressive motility; c, nonprogressive motility; and d, immotility. We evaluated at least 200 spermatozoa in at least five fields of vision. Sperm vitality, the percentage of motile or live sperm in a sample, was assessed approximately 200 spermatozoa stained by eosin–nigrosin at ×1000 magnification in oil immersion. Sperm morphology was observed in sperm smears stained with Giemsa (Singla *et al.*, 2013). Deformity rate was calculated (head defects, neck, and midpiece defects, tail defects, excess residual cytoplasm), assessing approximately 200 spermatozoa for the percentages of normal and abnormal forms.

Statistical analysis

Data were presented as mean ± SE. Statistical analysis was performed using SPSS 13.0 for Windows. We performed two-way ANOVA to examine the effects of dosage and treatment time of cabergoline on serum hormone concentrations, body and organ weight, and sperm density and quality. Least significant difference (LSD) test was then performed to determine the changes among the different groups, particularly between the males in the control group and the treatment groups. $P < 0.05$ was considered significant.

RESULTS

Sex hormones

FSH concentration was not affected by the dosage of cabergoline or time course ($P > 0.05$, Fig.1a). By contrast, LH concentration was significantly affected by the dosage of cabergoline ($F_{2,28} = 6.400$, $P = 0.005$) and by time course ($F_{2,28} = 4.616$, $P = 0.019$). The male rats treated with 100 μg/kg cabergoline showed evidently lower LH concentration than the rats in the control group or 50 μg/kg group (Fig. 1b). PRL concentration was not significantly affected by the different dosages of cabergoline ($P > 0.05$), but was possibly affected by time course after treatment ($F_{2,28} = 2.868$, $P = 0.074$, Fig. 1c). Testosterone level was also significantly lower by 48.6% in the group treated with 100 μg/kg cabergoline at 7 d ($P = 0.042$) and was fully restored at 24 d ($P > 0.05$, Fig. 1d) compared with that of the control group.

Body weight and reproductive organ mass

The body weight of the lesser rice-field rats treated with 50 or 100 μg/kg cabergoline showed no difference between the control and treatment groups during the entire experiment ($P > 0.05$). The dosage of cabergoline and time after treatment did not affect the wet weight of the epididymis, testis, and seminal vesicle ($P > 0.05$). The epididymis ($P = 0.037$) and testis ($P = 0.044$) of the male rats treated with 50 μg/kg cabergoline were lighter than those of the control males at 24 d after cabergoline treatment (Table I).

Sperm quality

Cabergoline dosage did not directly affect sperm density ($F_{2,30} = 0.564$, $P = 0.575$) and deformity rate ($F_{2,30} = 1.510$, $P = 0.237$), but time course after treatment significantly affected these parameters ($F_{2,30} = 5.392$, $P = 0.010$; $F_{2,30} = 5.736$, $P = 0.008$, respectively). The sperm density of rats treated with 50 μg/kg cabergoline was reduced by 24.3% at 24 d compared with that at 7 d after treatment ($P = 0.028$, Table II). The sperm deformity rate almost doubled (from 10% to 20%) in the 100μg/kg group than that in the control group at 7 d after treatment ($P = 0.004$). Furthermore, sperm deformity rate returned to the same level as the control group at 24 d ($P > 0.05$, Table II). Drug dosage ($F_{2,30} = 7.236$, $P = 0.003$) and time course ($F_{2,30} = 4.306$, $P = 0.023$) significantly affected male sperm vitality. At 50 μg/kg cabergoline, sperm

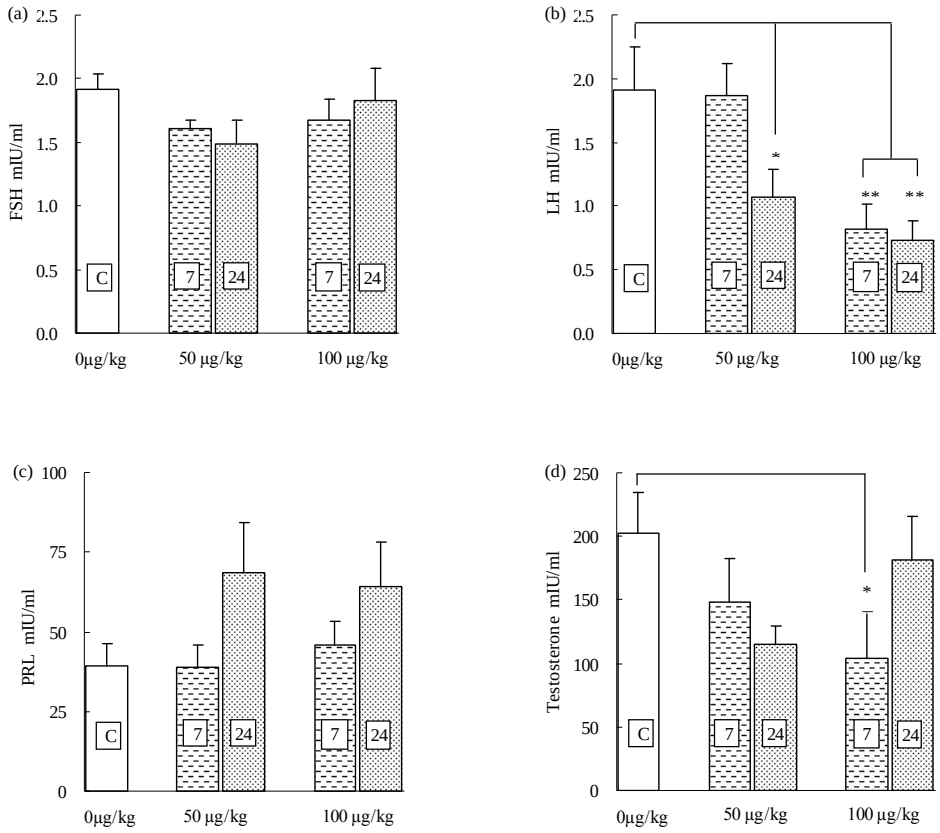

Fig. 1. Effects of cabergoline on serum concentrations of follicle-stimulating hormone (a), luteinizing hormone (b), prolactin (c) and testosterone (d) in male lesser rice-field rats. Mean (± SE) differences between groups were tested by LSD, * $P < 0.05$, ** $P < 0.01$. Rats were divided into five groups (n = 8 per group): the control group (C) and 50 μg/kg and 100 μg/kg treatment groups.

vitality was significantly reduced 28% ($P = 0.010$) at 7 d and 22% ($P = 0.032$) at 24 d compared with that of the control group (Table II).

Drug dosage and time course after treatment significantly affected "rapid progressive motility" (dosage: $F_{2,30} = 38.493$, $P < 0.001$; time: $F_{2,30} = 39.014$, $P < 0.001$), "slow or sluggish progressive motility" (D: $F_{2,30} = 21.005$, $P < 0.001$; T: $F_{2,30} = 21.957$, $P < 0.001$), and "immotility" sperms (dosage: $F_{2,30} = 20.598$, $P < 0.001$; time: $F_{2,30} = 21.225$, $P < 0.001$). The number of "rapid progressive motility" and "slow or sluggish progressive motility" sperms in the treatment groups was lower than that in the control group ($P < 0.001$). The number of "immotility" sperm in the treatment groups was higher than that in the control group ($P < 0.001$; Table II).

DISCUSSION

Cabergoline is well known as a PRL-inhibiting factor agonist in female and male, but we failed to find the decline of PRL concentration in male *R. losea* at 7 or 24 days after 50 or 100μg/kg cabergoline treatment. Our result probably was partly attributed to selection the dosage and the time course of cabergoline, and PRL measurement time points in the present study, since PRL was a pulsatile secretion and pleiotropic neuroendocrine hormone (Koch *et al.*, 2006; Grattan and Kokay, 2008). Moreover, there is difference of regulation pattern in PRL among varied species (Freeman *et al.*, 2000; Grattan and Kokay, 2008). The testosterone concentration of male *R. losea* treated with 100 μg/kg cabergoline at 7 d was

Table I.- Reproductive organ mass of male lesser rice-field rats (*Rattus losea*).

Dose	0 μg/kg	50 μg/kg		100 μg/kg	
Time(day)	C	7	24	7	24
Epididymis(g)	1.91±0.05^{a}	1.84±0.13^{a}	1.82±0.09^{a}	1.49±0.20^{b}	1.77±0.14^{a}
Testis(g)	4.02±0.23^{a}	3.77±0.26^{a}	3.55±0.15^{a}	3.10±0.50^{b}	4.04±0.22^{a}
Seminal vesicle(g)	2.03±0.07	2.46±0.35	2.14±0.15	1.94±0.31	1.94±0.30

Data are the mean ± SE. Means with different superscript letters vary significantly at $P < 0.05$ by LSD. Rats were divided into the control group (C) and 50 μg/kg and 100 μg/kg treatment groups (n = 8 per group).

Table II.- Sperm density, vitality, morphology and motility of male lesser rice-field rats (*Rattus losea*).

Dose		0 μg/kg	50 μg/kg		100 μg/kg	
Time(day)		C	7	24	7	24
Density×10^{6}		284.6±11.1^{abc}	325.3±25.6^{a}	323.3±24.7^{ab}	246.3±37.7^{c}	250.5±9.8^{bc}
Vitality %		91.4±1.6^{a}	63.4±3.3^{b}	84.3±1.6^{ab}	69.1±13.8^{b}	92.9±1.2^{a}
Deformity %		10.6±1.2^{b}	13.2±1.5^{b}	20.0±4.0^{a}	9.9±2.1^{b}	9.3±0.9^{b}
Motility %	Rapid progressive	30.7±4.2^{a}	12.9±1.5^{b}	8.6±0.8^{bc}	8.8±2.3^{bc}	3.9±1.0^{c}
	Slow or sluggish progressive	22.8±3.0^{a}	12.1±1.2^{b}	9.5±1.3^{b}	8.8±2.0^{b}	6.9±1.3^{b}
	Non-progressive	15.6±2.3^{a}	11.4±1.2^{abc}	7.4±1.4^{bc}	6.1±1.4^{c}	13.7±3.7^{ab}
	Immotility	30.8±9.0^{b}	63.7±3.8^{a}	74.4±2.6^{a}	76.4±5.4^{a}	75.5±5.7^{a}

Data are the mean ± SE. Means with different superscript letters vary significantly at $P < 0.05$ by LSD. Rats were divided into the control group (C) and 50 μg/kg and 100 μg/kg treatment groups (n = 8 per group).

significantly decreased by 48.6% compared with that in the control group, which suggested that PRL may play an important role in the secretion of testosterone, like in the human testes in vivo (Oseko *et al.*, 1991). In male dogs, cabergoline may suppress the pulse frequency of testosterone (Hess, 2006; Koch *et al.*, 2006). However, bromocriptine can increase the plasma levels of testosterone in male mice at higher doses (Rao *et al.*, 1984). It needs more study in varied doses and species to explore the effect of dose and species on regulation of cabergoline to testosterone.

LH concentration in this study was significantly reduced with increasing dosage of cabergoline and time course. Since PRL can suppress both frequency and amplitude of LH pulses and induce the pituitary gland to suppress LH secretion (Grattan and Kokay, 2008), the decrease of PRL reduced pituitary LH release and level of testosterone, and attenuated dopaminergic activity. Our current results imply that the change in LH may be sensitive to PRL increase at 24 d after cabergoline treatment. Alternatively, the reduction in plasma LH levels could be attributed to the changes in either pituitary or hypothalamic feedback. Moreover, the regulation of hypothalamic neurons or other neuronal products affecting LH release could be affected by cabergoline. The hypothalamic DA content was unevaluated in the present experiment, which reflected neuronal activity, and additional studies measuring DA need to be completed to address this question.

The effect of cabergoline on the testicular and epididymal functions in normal animals or humans remains unclear. In male *R. losea*, cabergoline elicited no dose-dependent effect on wet weight of reproductive organs. By contrast, the male rats treated with 50 μg/kg cabergoline exhibited lighter epididymis and testis than the control group at 24 d after cabergoline treatment. However, the growth of seminal vesicles and ventral prostate were affected in PRL gene knockout male mice (Steger *et al.*, 1998). The present results showed that there were no significant differences between normal males and cabergoline treatment. Therefore, seminal vesicles were not influenced; the weight of epididymis and testis reduced may be attributed to the decline of plasma testosterone levels in male rat treated by

cabergoline. Further studies should be conducted to determine the specific effects of cabergoline on male reproductive organs.

Cabergoline may improve sperm motility and morphology of dogs with poor sperm quality and increases sperm count in hyperprolactinemic patients (Ormandy *et al.*, 1997; De Rose *et al.*, 1998, 2003; Hess, 2006). This drug also allows multiple orgasms in rapid succession in normal male humans (Krüger *et al.*, 2003; Egli *et al.*, 2010). However, our data indicated that cabergoline did not increase the sperm density in healthy male *R. losea* but significantly weakened sperm activity and decreased sperm quality. The impaired sperm vitality and quality can be attributed to the decrease in LH levels after cabergoline treatment, since FSH, LH, and testosterone are necessary to initiate and maintain normal spermatogenesis (Meisel *et al.*, 1988; Schaison *et al.*, 1993).

The present results showed that cabergoline played physiological roles in the control of LH and testosterone release, the regulation of growth of the reproductive organs and impairing sperm quality in the male *R. losea*, which exhibited weakening reproductive functions in normal males. So it hinted that the using cabergoline repeatedly should exercise caution for normal male human who want to rise the libido for multiple orgasms in rapid succession, and for male animals that are needed to improve sperm count and quality. For using cabergoline as potential sterilant in fertility control further laboratory and field studies should be conducted to determine the antifertility effect of this drug on more species.

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