Effects of cabergoline on reproduction in three families of Australian marsupials

C. M. Hearn¹, G. Shaw¹, R. V. Short² and M. B. Renfree¹

¹Department of Zoology and ²Department of Obstetrics and Gynaecology, University of Melbourne, Parkville, Victoria 3052, Australia

The effects of the prolactin inhibiting drug, cabergoline, on pregnant and lactating marsupials were investigated in four species from three diverse families: the tammar wallaby, *Macropus eugenii*, the quokka, *Setonix brachyurus*, the brushtail possum, *Trichosurus vulpecula*, and the fat-tailed dunnart, *Sminthopsis crassicaudata*. In tammar wallabies, 20 µg cabergoline kg⁻¹ injected intramuscularly 1 day before expected birth did not alter the timing of parturition but neonates died within a day of birth, suggesting that the onset of lactation was compromised. During early lactation in tammars (56–69 days post partum), an intramuscular injection transiently retarded growth of the young, although they subsequently survived. This treatment induced reactivation of the quiescent corpus luteum and the blastocyst from diapause, so a new birth occurred 26–27 days later, despite the continued sucking of the young in the pouch. Intramuscular injection during late lactation (166–199 days post partum) apparently suppressed milk secretion since pouch young lost up to 20% of their bodyweight or died within 7 days of treatment. Oral administration of cabergoline had no effect on the growth of the young or on the quiescent corpus luteum and diapausing blastocyst. Quokkas showed similar responses to tammars after treatment in late lactation. Possums and dunnarts were less sensitive to injected cabergoline than the two macropodid species, and possums showed no response to oral administration. The lack of response of these marsupial species to oral cabergoline treatment suggests that accidental ingestion of baits, containing 20 µg cabergoline kg⁻¹, used to control introduced eutherian pests such as the red fox, *Vulpes vulpes*, or the feral cat, *Felis cattus*, should not affect the reproduction of native marsupials.

Introduction

Cabergoline is a synthetic dopamine agonist which suppresses prolactin secretion from the anterior pituitary in a number of eutherian mammals, including rats, dogs, cats, foxes and humans (Di Salle *et al.*, 1983; Post *et al.*, 1988; Jochle and Jochle, 1993; Onclin *et al.*, 1993; Ferrari *et al.*, 1995; Ferraro *et al.*, 1995; Marks *et al.*, 1996). Bromocriptine has been widely used as a dopamine agonist (Vance *et al.*, 1984) but, in clinical trials in humans, it is not as potent, long-lasting or well tolerated as the ergot derivative, cabergoline (Rolland *et al.*, 1991; Ferrari *et al.*, 1995).

In humans, a single oral dose of 10 µg cabergoline kg⁻¹ causes maximal inhibition of serum prolactin concentrations within hours of treatment, and the effect is sustained for at least 7 days (Pontiroli *et al.*, 1987; Rolland *et al.*, 1991; Ferrari *et al.*, 1995). Oral treatment of beagle bitches during late pregnancy with 5 µg cabergoline kg⁻¹ causes a decrease in prolactin to basal concentrations within 24 h, inducing premature luteolysis and abortion (Post *et al.*, 1988). Similarly, oral administration of 20 µg cabergoline kg⁻¹ to red foxes, *Vulpes vulpes*, signifi-

cantly reduces prolactin concentrations (Cowley, 1993) and causes a significant decline in cub activity, expected to be a consequence of increased abortion (Marks *et al.*, 1996). In lactating rats, dogs and cats, both oral and i.m. treatment with cabergoline inhibits prolactin secretion and effectively reduces or terminates milk production, thereby retarding growth of young (Jochle *et al.*, 1989; Ferraro *et al.*, 1995). The effect of prolactin-inhibiting drugs during lactation in ruminant animals is less well defined. In cattle, sheep and goats, intramuscular injection of bromocriptine immediately pre partum will inhibit prolactin secretion and prevent the onset of lactation but, if administered post partum when lactation is established, milk yield remains unchanged (Hart, 1973; Smith *et al.*, 1974).

Nothing is known about the effects of cabergoline on reproduction in marsupials. Bromocriptine injection in the tammar wallaby, *Macropus eugenii*, inhibits prolactin secretion without affecting parturition, induces reactivation of the quiescent corpus luteum and diapausing blastocyst, and inhibits lactation (Tyndale-Biscoe and Hinds, 1984; Fletcher *et al.*, 1990; Renfree *et al.*, 1994). Similarly, in the Bennett's wallaby, *Macropus rufogriseus rufogriseus*, Western grey kangaroo, *Macropus fuliginosus*, and Eastern grey kangaroo, *Macropus giganteus*, i.m. bromocriptine terminates lactation, causing

Received 1 September 1997.

growth retardation or death of the pouch young (Curlew *et al.*, 1986; Loudon and Brinklow, 1990; Hinds and Tyndale-Biscoe, 1994). As in the macropodid marsupials (Hinds and Tyndale-Biscoe, 1985; Muths and Hinds, 1996), in the dasyurids (Hinds and Merchant, 1986) and phalangerids (Hinds and Janssens, 1986) plasma prolactin concentrations are low during early lactation, when poikilothermic young are permanently attached to the teat and milk production is low (Tyndale-Biscoe and Renfree, 1987). Prolactin increases during late lactation, with the rapid increase in milk production and growth rate of the young (Tyndale-Biscoe and Renfree, 1987). The effects of inhibiting prolactin during lactation on pouch young growth in these non-macropodid marsupials has not been investigated.

The importance of prolactin for reproduction in both eutherian and marsupial mammals (Cowie, 1984; Tyndale-Biscoe and Renfree, 1987) suggests that drugs that inhibit prolactin secretion could be used to inhibit reproduction in mammalian pest species. Cabergoline impregnated in a meat bait is very effective in inducing abortion and inhibiting lactation in cats (Jochle and Jochle, 1993) and foxes (Marks *et al.*, 1996), two of the principal mammalian pest species in Australia. Therefore, it is important to determine whether accidental ingestion of cabergoline baits has any adverse effects on the reproduction of native marsupial species. Furthermore, one marsupial introduced to New Zealand, the brushtail possum, *Trichosurus vulpecula*, is now a major pest (Cowan and Tyndale-Biscoe, 1997) and oral baiting with cabergoline might be a useful way of controlling reproduction in this species. The aim of this study was to investigate the effects of cabergoline on the reproduction of four representative Australian marsupial species from three families, two macropodids: the tammar wallaby and the quokka, *Setonix brachyurus*; one phalangerid: the brushtail possum; and one dasyurid: the fat-tailed dunnart, *Sminthopsis crassicaudata*.

Materials and Methods

Animals

Adult female tammar wallabies (*Macropus eugenii*) (4.0–5.9 kg bodyweight), originating from Kangaroo Island, South Australia, were maintained with males in our breeding colony in open grassed enclosures at Clayton. Lucerne cubes, oats and water were available *ad libitum*. Pouch young were aged either from known birth dates or from head length measurements (Poole *et al.*, 1991). Adult female quokkas (*Setonix brachyurus*) (2.6–3.7 kg) of Rottnest Island, West Australia origin, were also held in our breeding colony as described above. Pouch young were aged from pes and tail length (Shield and Woolley, 1961). Brushtail possums (*Trichosurus vulpecula*) (1.7–3.2 kg) were captured at Werribee, Victoria in cage traps baited with apple and peanut butter. Female possums were housed together with males in elevated nest boxes in outdoor pens, and fed on a diet of fresh fruits and vegetables, oats, and dry dog biscuits. Eucalyptus branches and leaves were also made available. Water was provided *ad libitum*. Pouch young were aged from head length measurements (Lyne and Verhagen, 1957). Fat-tailed dunnarts

(*Sminthopsis crassicaudata*) (14.0–20.0 g) were purchased from the breeding colony at the Laboratory of Animal Services, University of Adelaide, South Australia. Females carrying pouch young (with a litter size ranging from one to five) were housed individually in breeding boxes as described by Bennett *et al.* (1990). Pouch young were aged from known dates of birth.

All animals were monitored each day. No adverse reactions to treatment were observed in any of the adult animals. Pouch young were removed from the teat, or the nest in the case of the dunnarts, so that measurements could be taken. The changing weight of each young was used as an indirect measure of milk production. Young that lost $\geq 20\%$ of their initial bodyweight from the day of treatment were either killed by decapitation or, for larger young, by an i.p. injection of $> 100 \text{ mg kg}^{-1}$ of a 60 mg pentobarbitone ml^{-1} in saline solution.

During early lactation, tammar young are unable to reattach themselves to the teat so they were reattached manually, as described by Merchant and Sharman (1966), and checked each day to ensure that they remained attached. Possum pouch young were sufficiently developed to reattach to the teat themselves (Sharman, 1962), but were checked the day after measurement to ensure reattachment had been successful.

Husbandry and handling of all animals followed the guidelines of the National Health and Medical Research Council of Australia (1990). Experimental work was approved by the University of Melbourne Animal Experimentation Ethics Committee.

Treatments

Preparation of solutions. Cabergoline (1-[(6-allyl)ergolin-8 β -yl]carbonyl]-1-[3-(dimethylamino) propyl]-3-ethylurea), at a concentration of $50 \text{ } \mu\text{g ml}^{-1}$ in triacyl glycerol (Galastop), was a gift from Centralvet Ltd, Milan. Cabergoline ($20 \text{ } \mu\text{g kg}^{-1}$) was administered i.m. to all adult animals as a single dose, except where specified. This dose is higher than the maximum dose of $0.9 \text{ } \mu\text{g kg}^{-1}$ and $9.0 \text{ } \mu\text{g kg}^{-1}$ recommended for dogs and cats, respectively (Galastop; Centralvet Ltd., Milan, Italy), and is equivalent to the oral dose used to control the fertility of feral foxes (Marks *et al.*, 1996). Owing to the small size of the dunnarts, Galastop was diluted with peanut oil so that a convenient volume of solution could be injected. Control animals were treated with an equivalent volume of peanut oil. Cabergoline was administered orally through a syringe placed in the diastema of unsedated but restrained animals. The day of treatment was designated day 0.

Bromocriptine (CB154; 2-bromo- α -ergocryptine mesylate), a gift from Sandoz Pharmaceuticals, Sydney, was prepared and administered i.m. at a dose of 5 mg kg^{-1} , as described by Fletcher *et al.* (1990).

Treatment during late pregnancy. Pregnancy was initiated by removing pouch young (RPY) during late March from female tammars presumed to be carrying a blastocyst in lactational diapause. The gestation period after RPY is 26.4 ± 1.0 days (Tyndale-Biscoe and Renfree, 1987; Fletcher *et al.*, 1988) and all females have a postpartum oestrus 1 h after birth (Rudd, 1994).

The day of RPY was defined as day 0 of gestation. Adult tammar were injected i.m. with 20 µg cabergoline kg⁻¹ ($n = 6$), or with peanut oil ($n = 6$) on day 25 of gestation. Females were examined each day for the presence of newborn young or a copulatory plug from day 25 to day 31 after RPY. Young were checked each day for 3 days post partum.

Treatment during early lactation

Tammar wallaby. Female tammar, with young aged between 56 and 69 days (mean 62 days), were injected i.m. with 20 µg cabergoline kg⁻¹ ($n = 6$), 5 mg bromocriptine kg⁻¹ ($n = 2$) or peanut oil (controls, $n = 5$) during early April. Pouch young were weighed on days 0, 6, 9, 12 and 15 after treatment. Young were removed 23 days after treatment from females treated with cabergoline or bromocriptine, to allow room in the pouch for any newborn young. Females were checked from days 26 to 30 after treatment for the presence of newborn young or copulatory plugs. Young were monitored for several days after birth.

A further group of female tammar with pouch young, aged between 42 and 51 days (mean 48 days), ($n = 5$) were treated in early June with an oral dose of 20 µg cabergoline kg⁻¹. Young were weighed on days 0, 6, 9, 12 and day 15, when they were permanently removed. From days 26 to 30 after treatment females were checked for birth or copulatory plugs. Since none gave birth, all five animals were subsequently injected i.m. with 5 mg bromocriptine kg⁻¹, and their pouches were checked for the presence of a new young 31 days later to determine if they had been carrying a blastocyst.

Brushtail possum. Female possums, with young aged between 32 and 52 days (mean 42 days), were injected i.m. with either 20 µg cabergoline kg⁻¹ ($n = 6$) or with peanut oil ($n = 6$) in late May. The weight of the young was measured each week for 3 weeks after treatment. Control animals were subsequently injected i.m. with 40 µg cabergoline kg⁻¹, and animals were measured as before.

Treatment during late lactation

Tammar wallaby. Tammar carrying pouch young, aged between 166 and 199 days (mean 182 days), were allocated randomly to groups and treated with 20 µg cabergoline kg⁻¹ i.m. ($n = 5$) or orally ($n = 2$) during early August. The control group was injected with peanut oil ($n = 4$). Pouch young were weighed on days 0, 2, 4, 7, 11 and 14 after treatment.

Quokka. Quokkas carrying young aged between 137 and 156 days (mean 147 days) were either injected i.m. with 20 µg cabergoline kg⁻¹ ($n = 5$) or peanut oil ($n = 5$), or treated orally with 20 µg cabergoline kg⁻¹ ($n = 4$) in mid-August. Measurements were taken as described above for tammar.

Brushtail possum. Female possums, with pouch young aged between 107 and 135 days (mean 117 days), were injected i.m. with 20 µg cabergoline kg⁻¹ ($n = 4$), 40 µg cabergoline kg⁻¹ ($n = 4$) or peanut oil ($n = 4$), or were given 20 µg cabergoline

kg⁻¹ orally ($n = 3$) in mid-August. Weight was measured on days 0, 2, 4 and 7 after treatment.

Fat-tailed dunnart. Dunnarts were treated during late August, as soon as the young (aged between 44 and 55 days, mean 50 days) were seen in the nest. Adults were either injected i.m. with diluted Galastop (20 µg cabergoline kg⁻¹) ($n = 4$) or peanut oil ($n = 3$). In addition to the days of measurement described above for the possum, data were collected on days 9 and 11 after treatment.

Statistical analysis

The growth of pouch young after treatment was normalized as the percentage change in bodyweight relative to weight on the day of treatment, day 0. Results are expressed as the mean $\pm$ standard error of the percentage change in weight. Where a sample size of only two was present, the mean $\pm$ range of the percentage change in weight has been indicated. Differences between treatment groups over time were tested using repeated measures analysis of variance. Differences between treatments were regarded as significant when $P < 0.05$.

Results

Tammar wallaby

Effects of intramuscular injection during late pregnancy. Cabergoline treatment on day 25 of gestation did not affect the timing of parturition, with four of six cabergoline-treated animals giving birth at the normal time, on day 26.8 ± 0.2 SEM, and three of six control animals giving birth on day 27.0 ± 1.0 . One of the cabergoline treated females that did not give birth had a copulatory plug on day 31, consistent with a return to oestrus without pregnancy. None of the control animals was observed to mate or have a copulatory plug.

On the day of birth, all young were alive and attached to one of the four available teats. Within 24 h of birth, three of the four neonates from cabergoline-treated mothers were found dead in the pouch. The surviving neonate was born on day 28 of gestation, 1 or 2 days later than the other young. None of the three control pouch young died.

Effects of intramuscular injection during early lactation. The weight of pouch young from females treated with cabergoline or bromocriptine was significantly lower than that of control animals 6 and 9 days after treatment, respectively ($P < 0.05$) (Fig. 1a). One young from a cabergoline-treated adult was dehydrated and emaciated by day 3 after treatment and had lost 17% of its initial bodyweight within 6 days. Although this young remained attached to the teat, it continued to lose weight and was killed 8 days after treatment. All of the other females retained their young until they were permanently removed 23 days after treatment. Treatment with either cabergoline or bromocriptine caused reactivation of the blastocyst from diapause, and most treated females gave birth to a new young within days of removing the older pouch young. Birth occurred on day 26.8 ± 0.5 ($n = 4$) and day 28.0 ± 0.0

Fig. 1. Pouch young bodyweight (expressed as mean $\pm$ SEM, or mean $\pm$ range where $n = 2$, percentage of initial values) from the day of treatment, day 0, during (a) early lactation (62 ± 5 days) or (b) late lactation (182 ± 11 days) in tammar wallabies. Adults were treated with cabergoline ($20 \mu\text{g kg}^{-1}$ i.m., $\bullet$, $n = 6$ in early and $n = 5$ in late lactation), cabergoline ($20 \mu\text{g kg}^{-1}$ orally, $\square$, $n = 2$ in late lactation), bromocriptine (5 mg kg^{-1} i.m., $\blacktriangle$, $n = 2$ in early lactation), or peanut oil (control, $\circ$, $n = 5$ in early and $n = 4$ in late lactation). Numbers indicate decrease of pouch young. Asterisk and cross denote that values from cabergoline and bromocriptine treatment, respectively, are significantly different from controls ($P < 0.05$).

($n = 2$) after cabergoline or bromocriptine treatment, respectively. All these newborn young attached to one of the three unsucked teats and survived. The older young were not removed from the pouch of control females during this experiment, and none of the controls gave birth, suggesting that the suckling stimulus of the pouch young inhibited blastocyst reactivation.

Effects of oral treatment of cabergoline during early lactation. Four of five pouch young gained weight at a similar rate to

controls, with young gaining 31% and 73% of their initial bodyweight within 9 and 15 days, respectively, after oral treatment with cabergoline. One young lost 6% of its initial bodyweight by day 6 after treatment and died 5 days later. The mammary gland of the mother had not regressed and milk could be easily expressed from the teat, suggesting that her young had not died from failure of milk production. None of the females gave birth after oral treatment with cabergoline and, therefore, were treated with bromocriptine (i.m.). By 31 days after injection, four of five females had young < 5 days old, showing that they carried a diapausing blastocyst that had not reactivated with oral cabergoline treatment.

Effects of intramuscular and oral treatment during late lactation. Growth of pouch young from animals treated orally with cabergoline in late lactation was not significantly different from that of controls ($P > 0.05$). However, 7 days after i.m. treatment with cabergoline, pouch young growth was significantly lower than that of controls ($P < 0.0001$) (Fig. 1b). Three of five young from females treated i.m. with cabergoline either died in the pouch or were killed after losing up to 23% of their initial bodyweight within 7 days of the treatment. The two young that survived were the oldest treated, and both eventually resumed growth to parallel the controls by day 14 after treatment (Fig. 1b). This increase in weight coincided with observations of the two young grazing.

Quokka

Effects of intramuscular and oral treatment during late lactation. Pouch young lost a significant and rapid amount of weight after i.m. injection with cabergoline, which was not evident in young of control or orally treated females. All young from the i.m. treatment group were emaciated and lost at least 20% of their initial bodyweight within 6 or 7 days after the treatment ($P < 0.0001$) (Fig. 2). Young were either found dead or were killed 7 days after treatment. By contrast, young from control females and orally treated females gained an average of 10% of their initial bodyweight in the 7 days after treatment. Control pouch young were first seen out of the pouch 1 month after completion of the experiment.

Brushtail possum

Effects of intramuscular treatment during early lactation. Intramuscular treatment of cabergoline at a dose of $20 \mu\text{g kg}^{-1}$ had no significant effect on the weight of pouch young compared with that of controls ($P > 0.05$) (Fig. 3a). Similarly, pouch young of females treated with $40 \mu\text{g cabergoline kg}^{-1}$ showed a steady increase in weight both before and after treatment, and the weight of young increased by 60% in the 3 weeks after treatment. One control pouch young died in the pouch 21 days after treatment. The cause of death was not known, but the young was emaciated and had lost 33% of bodyweight within a week.

Effects of intramuscular and oral treatment during late lactation. Young from possums treated with $20 \mu\text{g cabergoline kg}^{-1}$, either i.m. or orally, gained weight at the same rate as the

Fig. 2. Pouch young bodyweight (expressed as mean $\pm$ SEM percentage of initial values) from the day of treatment, day 0, during late lactation (147 ± 5 days) in quokkas. Adults were treated with cabergoline ($20 \mu\text{g kg}^{-1}$ i.m., ●, $n=5$), cabergoline ($20 \mu\text{g kg}^{-1}$ orally, □, $n=4$), or peanut oil (control, ○, $n=5$). Numbers indicate decrease of pouch young. Asterisk denotes that values from i.m. cabergoline treatment are significantly different from controls ($P < 0.05$).

controls ($P > 0.05$). However, the increase in weight of young from adults administered $40 \mu\text{g kg}^{-1}$ cabergoline i.m. was significantly lower than that of controls 7 days after treatment ($P < 0.05$) (Fig. 3b). One young, from a female given $20 \mu\text{g kg}^{-1}$ cabergoline i.m., was found dead 2 days after treatment. This young was not emaciated and had lost only 5% of its initial bodyweight. However, the mammary gland of the female had regressed, suggesting that the young may have died from partial failure of lactation.

Fat-tailed dunnart

Effects of intramuscular treatment during late lactation. Cabergoline injection ($20 \mu\text{g kg}^{-1}$) had no significant effect on the increase in litter weight ($P > 0.1$) (Fig. 4). Two of four young from a control female died during the experiment. Neither young was found in the nest box or cage, suggesting that the mother had eaten both, a behaviour that has been reported in females handled repeatedly. All other young were first seen eating solid food 5 days after completion of the experiment. The litter size of females differed, with some having only one young and others having litters of four or five. The effect of cabergoline treatment on different litter sizes could not be compared statistically owing to the small sample size.

Discussion

Cabergoline slowed the normal growth of tammar and quokka pouch young when administered i.m. at a dose of $20 \mu\text{g kg}^{-1}$, but was ineffective when given orally. Growth of the brushtail possum and fat-tailed dunnart young was not affected by an

Fig. 3. Pouch young bodyweight (expressed as mean $\pm$ SEM percentage of initial values) from the day of treatment, day 0, during (a) early lactation (53 ± 14 days) or (b) late lactation (117 ± 9 days) in the brushtail possum. Adults were treated with cabergoline ($20 \mu\text{g kg}^{-1}$ i.m., ●, $n=6$ in early and $n=4$ in late lactation), cabergoline ($40 \mu\text{g kg}^{-1}$ i.m., ■, $n=4$ in late lactation), cabergoline ($20 \mu\text{g kg}^{-1}$ orally, □, $n=3$ in late lactation), or peanut oil (control, ○, $n=6$ in early and $n=4$ in late lactation). Asterisk denotes that values from treatment i.m. with $40 \mu\text{g kg}^{-1}$ cabergoline are significantly different from controls ($P < 0.05$).

equivalent i.m. dose of cabergoline, although growth was retarded in the possum young when double this dose was injected during late lactation.

In pregnant tammar, cabergoline did not alter the timing of parturition, but young died within a day of birth. Intramuscular administration of bromocriptine towards the end of gestation has similar effects (Fletcher *et al.*, 1990). A prepartum surge in prolactin is essential for mammary gland development and the initiation of lactation in a number of eutherian species (Kann and Denamur, 1974; Karg and Schams, 1974). In cats treated with cabergoline in late pregnancy, mammary glands regress

Fig. 4. Pouch young bodyweight (expressed as mean $\pm$ SEM percentage of initial values) from the day of treatment, day 0, during late lactation (50 ± 4 days) in fat-tailed dunnarts. Adults were treated with cabergoline ($20 \mu\text{g kg}^{-1}$ i.m., ●, $n = 4$, total young $n = 14$) or peanut oil (control, ○, $n = 3$, total young $n = 9$). There was no significant difference between the treatment and control groups.

and the newborn young cannot be suckled (Jochle and Jochle, 1993). Similarly, rats treated with cabergoline in late pregnancy are unable to lactate and their pups die within 12 h of birth (Ferraro *et al.*, 1995). The high mortality of tammar neonates after cabergoline or bromocriptine treatment supports the hypothesis that a prepartum pulse of prolactin (Tyndale-Biscoe *et al.*, 1983) is essential for the establishment of lactation in this marsupial species (Fletcher *et al.*, 1990; Renfree *et al.*, 1994).

A single injection of cabergoline to female tammars was sufficient to induce reactivation of their blastocysts from embryonic diapause. Blastocyst reactivation also occurs if the sucking stimulus of the young is removed for at least 72 h during early lactation (Gordon *et al.*, 1988), or if prolactin is suppressed for ≥ 3 days consecutively (Hinds, 1994). This suggests that the effect of a single injection of cabergoline must last for ≥ 3 days in tammars. However, the effect of treatment is only transient, as the neonates born 26 days later survive. In Bennett's wallabies, bromocriptine suppresses prolactin for approximately 6 days (Curlewis *et al.*, 1986; Loudon and Brinklow, 1990). In contrast, oral administration of cabergoline in tammars did not induce blastocyst reactivation, yet the blastocysts remained viable as a subsequent injection of bromocriptine induced birth 1 month later.

During early lactation, i.m. cabergoline and bromocriptine transiently retarded growth of tammar young for up to 9 days. This result is consistent with a decrease in plasma prolactin concentrations (Tyndale-Biscoe and Hinds, 1984; Curlewis *et al.*, 1986; Loudon and Brinklow, 1990). After hypophysectomy, which presumably completely removes prolactin, lactation ceases and young died within days (Hearn, 1974).

During late lactation, a single injection of cabergoline in both tammars and quokkas resulted in significant weight loss or death of most young. Similarly, pouch young growth was

retarded and death occurred within 3 weeks of a single bromocriptine injection in Western grey and Eastern grey kangaroos, and in tammar and Bennett's wallabies (Tyndale-Biscoe and Hinds, 1984; Curlewis *et al.*, 1986; Hinds and Tyndale-Biscoe, 1994). The rapid resumption in growth of the two oldest tammar young, 7 days after cabergoline injection, may be a result of grazing and the only temporary inhibition of milk secretion by cabergoline.

Neither tammar nor quokka young were affected by cabergoline given orally. In contrast, in dogs and cats, oral treatment is as effective as injection (Jochle *et al.*, 1989). Bromocriptine is also apparently inactive orally in the tammar, and Hinds and Tyndale-Biscoe (1994) suggest that this is due to inactivation of alkaloids in their ruminant-like fore stomach.

In brushtail possums, i.m. injection with $20 \mu\text{g}$ cabergoline kg^{-1} had no effect on pouch young growth during early or late lactation, but double this dose in late lactation transiently slowed their growth. This shows that possums are less sensitive to cabergoline treatment than are tammars and quokkas. A strong dose-related association between cabergoline and lactation inhibition is evident in eutherian species, including lactating dogs (Jochle *et al.*, 1989) and rats (Ferraro *et al.*, 1995).

During late lactation in fat-tailed dunnarts, i.m. cabergoline did not inhibit the growth of the young, and so their response may, like that of possums, be dose-related. Since the prolactin profile of dasyurids is similar to that of other marsupials (Hinds and Merchant, 1986), inhibition of prolactin would be expected to decrease or terminate lactation. Further studies are necessary to determine whether oral or higher doses of cabergoline have any effect on the reproduction of this carnivorous species. In addition, testing the effects of cabergoline during early and late lactation in a larger carnivorous marsupial, such as the eastern quoll, *Dasyurus viverrinus*, which has a digestive system similar to that of dogs and cats (Hume, 1982), would be of further benefit for determining the consequences of baiting.

Cabergoline can be used to induce abortion or terminate lactation in a number of eutherians, including dogs, cats and foxes (Onclin *et al.*, 1993; Jochle *et al.*, 1989; Marks *et al.*, 1996). Red foxes and feral cats are major pests in Australia, where they threaten the survival of many native animals. Baiting with cabergoline is an effective and humane way to control populations of these introduced pests (Marks *et al.*, 1996). Since marsupial reproduction is unaffected by oral administration of this drug at the doses tested in this study, it would be of little use in the control of brushtail possum pest populations in New Zealand. However, cabergoline baits used as a strategy to control fox or feral cat populations in Australia are unlikely to have adverse effects on the reproduction of non-target marsupial species.

The authors thank R. L. C. Moyle and H. L. Chapman for their assistance with all aspects of animal handling and husbandry during these experiments. The authors are also grateful to Upjohn-Pharmacia Australia for the kind gift of Galastop and to Sandoz Pharmaceuticals for the gift of bromocriptine. Animals were captured and held under permits from the Department of Conservation and Natural Resources, Victoria (Permit Numbers RP-95-087: *Setonix brachyurus*; RP-95-088: *Macropus eugenii*; RP-96-063: *Trichosurus vulpecula*; and IM-96-010636: *Sminthopsis crassicaudata*).

References

- Bennett JH, Breed WG, Hayman DL and Hope RM (1990) Reproduction and genetical studies with a laboratory colony of the dasyurid marsupial *Sminthopsis crassicaudata*. *Australian Journal of Zoology* **37** 207–222
- Cowan PE and Tyndale-Biscoe CH (1997) Australian and New Zealand mammal species considered to be pests or problems *Reproduction, Fertility and Development* **9** 27–36
- Cowie AT (1984) Lactation. In *Reproduction in Mammals: Hormonal Control of Reproduction* pp 195–231 Eds CR Austin and RV Short. Cambridge University Press, Cambridge
- Cowley M (1993) *Reproductive Control of Foxes* BSc Honours Thesis, Monash University, Clayton
- Curlewis JD, Whitle AS, Loudon SI and McNeilly AS (1986) Effects of lactation and response to bromocriptine during lactation in the Bennett's wallaby (*Macropus rufogriseus rufogriseus*) *Journal of Endocrinology* **110** 56–66
- Di Salle E, Ornati G, Guidici D and Briatico G (1983) Prolactin lowering effect of a new ergoline derivative, FCE 21336, in the rat. A comparison with bromocriptine *Acta Endocrinologica* **103** Supplement **256** 265
- Ferrari C, Piscitelli G and Crosignani PG (1995) Cabergoline – a drug for the treatment of hyperprolactinaemia *Human Reproduction* **10** 1647–1652
- Ferraro F, Nisoli LGS, Salvo R, Maffeo G and Jochle W (1995) Periodic use of cabergoline, a prolactin inhibitor, for control of reproductive success in rats – work in progress *Theriogenology* **44** 1–7
- Fletcher TP, Jettton AE and Renfree MB (1988) Influence of progesterone and oestradiol-17 β on blastocysts of the tammar wallaby during seasonal diapause *Journal of Reproduction and Fertility* **83** 193–200
- Fletcher TP, Renfree MB and Shaw G (1990) Effects of bromocriptine at parturition in the tammar wallaby, *Macropus eugenii*. *Reproduction, Fertility and Development* **2** 79–88
- Gordon K, Fletcher TP and Renfree MB (1988) Reactivation of the quiescent corpus luteum and diapausing embryo after temporary removal of the sucking stimulus in the tammar wallaby, *Macropus eugenii*. *Journal of Reproduction and Fertility* **83** 401–406
- Hart IC (1973) Effects of 2-bromo- α -ergocryptine on milk yield and the level of prolactin and growth hormone in the blood of the goat at milking *Journal of Endocrinology* **57** 179–180
- Hearn JP (1974) The pituitary gland and implantation in the tammar wallaby, *Macropus eugenii*. *Journal of Reproduction and Fertility* **39** 235–241
- Hinds LA (1994) Prolactin, a hormone for all seasons: endocrine regulation of seasonal breeding in the Macropodidae *Oxford Reviews of Reproductive Biology* **16** 249–301
- Hinds LA and Janssens PA (1986) Changes in prolactin in peripheral plasma during lactation in the brushtail possum, *Trichosurus vulpecula*. *Australian Journal of Biological Science* **39** 171–178
- Hinds LA and Merchant JC (1986) Plasma prolactin concentrations throughout lactation in the Eastern Quoll, *Dasyurus viverrinus* (Marsupialia: Dasyuridae) *Australian Journal of Biological Science* **39** 179–186
- Hinds LA and Tyndale-Biscoe CH (1985) Seasonal and circadian patterns of circulating prolactin during lactation and seasonal quiescence in the tammar wallaby, *Macropus eugenii*. *Journal of Reproduction and Fertility* **74** 173–183
- Hinds LA and Tyndale-Biscoe CH (1994) The effects of bromocriptine on lactation and subsequent reproduction in grey kangaroos, *Macropus fuliginosus* and *Macropus giganteus*. *Reproduction, Fertility and Development* **6** 705–711
- Hume ID (1982) *Digestive Physiology and Nutrition of Marsupials* Cambridge University Press, Cambridge
- Jochle W and Jochle M (1993) Reproduction in a feral cat population and its control with a prolactin inhibitor (Cabergoline) *Journal of Reproduction and Fertility Supplement* **47** 419–424
- Jochle W, Arbeiter K, Post K, Ballabio R and D'Ver AS (1989) Effects on pseudopregnancy, pregnancy and interoestrous intervals of pharmacological suppression of prolactin secretion in female dogs and cats *Journal of Reproduction and Fertility Supplement* **39** 199–207
- Kann G and Denamur R (1974) Possible role of prolactin during the oestrus cycle and gestation in the ewe *Journal of Reproduction and Fertility* **39** 473–483
- Karg H and Schams D (1974) Prolactin release in cattle *Journal of Reproduction and Fertility* **39** 463–472
- Loudon SI and Brinklow BR (1990) Melatonin implants prevent the onset of seasonal quiescence and suppresses the release of prolactin in response to a dopamine antagonist in the Bennett's wallaby (*Macropus rufogriseus rufogriseus*) *Journal of Reproduction and Fertility* **90** 611–618
- Lyne AG and Verhagen AMW (1957) Growth of the marsupial *Trichosurus vulpecula* and a comparison with some higher mammals *Growth* **21** 167–195
- Marks CA, Nijk M, Gigliotti F, Busana F, and Short RV (1996) Preliminary field assessment of a cabergoline baiting campaign for reproductive control of the Red Fox (*Vulpes vulpes*) *Wildlife Research* **23** 161–168
- Merchant JC and Sharman GB (1966) Observations on the attachment of marsupial pouch young by fostering mothers of the same or different species *Australian Journal of Zoology* **14** 593–609
- Muths E and Hinds LA (1996) Circulating levels of prolactin and progesterone in a wild population of red kangaroos (*Macropus rufus*) *General Comparative Endocrinology* **103** 317–322
- National Health and Medical Research Council (1990) *A Guide to Use of Australian Native Mammals in Biomedical Research* Australian Government Publishing Service, Canberra
- Onclin K, Silva LDM, Donnay I and Verstegen JP (1993) Luteotrophic action of prolactin in dogs and the effects of a dopamine agonist, cabergoline *Journal of Reproduction and Fertility Supplement* **47** 403–409
- Pontiroli AE, Viberti GC, Mangili R, Cammelli L and Dubini A (1987) Selective and extremely long inhibition of prolactin release in man by 1-ethyl-3-(3'-dimethyl-aminopropyl)-3-(6'-alkaline-8'- β -carbonyl)-urea-diphosphate (FCE 21336) *British Journal of Clinical Pharmacology* **23** 433–438
- Poole WE, Simms NG, Wood JT and Lubulwa M (1991) Tables for age determination of the Kangaroo Island wallaby (tammar), *Macropus eugenii*, from body measurements *CSIRO Division of Wildlife and Ecology, Technical Memorandum Number* 31
- Post K, Evans LE and Jochle W (1988) Effect of prolactin suppression with cabergoline on the pregnancy of the bitch *Theriogenology* **29** 1233–1243
- Renfree MB, Shaw G and Fletcher TP (1994) Evidence for the essential role of prostaglandins for parturition in a marsupial, *Macropus eugenii*. *Journal of Reproduction and Fertility* **102** 433–446
- Rolland R, Piscitelli G, Ferrari C and Petroccione A (1991) Single dose cabergoline versus bromocriptine in inhibition of puerperal lactation: randomised, double blind, multicentre study *British Medical Journal* **302** 1367–1371
- Rudd CD (1994) *Sex Differences in the Tammar Wallaby*, *Macropus eugenii*. PhD thesis, Monash University, Clayton
- Sharman GB (1962) The initiation and maintenance of lactation in the marsupial *Trichosurus vulpecula*. *Journal of Endocrinology* **25** 375–385
- Shield JW and Woolley P (1961) Age estimation by measurement of pouch young of the quokka (*Setonix brachyurus*) *Australian Journal of Zoology* **9** 14–23
- Smith VG, Beck TW, Convey EM and Tucker HA (1974) Bovine serum prolactin, growth hormone, cortisol and milk yield after ergocryptine *Neuroendocrinology* **15** 172–181
- Tyndale-Biscoe CH, Linds LA, Horn CA and Jenkin G (1983) Hormonal changes at oestrus, parturition and post-partum oestrus in the tammar wallaby (*Macropus eugenii*) *Journal of Endocrinology* **96** 155–161
- Tyndale-Biscoe CH and Hinds LA (1984) Seasonal patterns of circulating progesterone and prolactin in response to bromocriptine in the female tammar, *Macropus eugenii*. *General and Comparative Endocrinology* **53** 58–68
- Tyndale-Biscoe CH and Renfree MB (1987) *Reproductive Physiology of Marsupials*. Cambridge University Press, Cambridge
- Vance ML, William S, Evans MD and Thorner MO (1984) Bromocriptine *Annals of Internal Medicine* **100** 78–91