Effects of exogenous amines on reproduction in female Angora goats[1,2]

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An investigation was conducted into the effects of two phenolic amines, *N*-methyl-β-phenethylamine (NMP) and tyramine (T) on corpus luteum function and reproductive performance of Angora goats. Both compounds are widely distributed through the plant kingdom and, because of their sympathomimetic action, may interfere with normal reproductive processes. In Experiment 1, 20 nannies ($\bar{x}$ = 26.7 ± 0.96 kg) received either 0, 1, 2, or 4 mg NMP in 2 ml corn oil/kg BW daily, for 45 days. In Experiment 2, 75 nannies ($\bar{x}$ = 32.1 ± 0.46 kg) received either 3, or 6 mg/kg BW NMP in 2 ml corn oil; 1, or 3 mg/kg BW T in physiological saline, or 2 ml corn oil (control) daily, for 45 days. In both studies treatments were administered by i.v. injection. Mating was by natural service, beginning after the start of treatment. Jugular blood samples were collected weekly, processed to yield serum, and serum progesterone (P4) concentrations were determined by radioimmunoassay (RIA). In Experiment 1, no dose response was detected but P4 concentrations were reduced (P = 0.03) in the treated animals. In Experiment 2, no dose response was detected but P4 concentrations in NMP-treated animals (3.87 ± 0.618) were lower (P = 0.05) than in the control (5.65 ± 0.747) or in T-treated animals (4.73 ± 0.528, P = 0.08). No difference in P4 concentrations was detected between T-treated and control animals (P = 0.59). Fewer NMP-treated nannies became pregnant (59%) than either control (77%) or T-treated nannies (88%) (P = 0.053). The results show that exogenous phenolic amines vary in their effect on reproductive performance of nannies.

'n Ondersoek is geloods na die invloed van twee fenolamiene, *N*-metiel-β-fenetielamien(NMP) en tiramien (T), op die corpus luteum-funksie en die voortplantingprestasie van Angora-bokke. Albei verbindings kom wyd verspreid in die planteryk voor en mag, weens hul simpatomimetiese werking, normale voortplantingprosesse beïnvloed. In Eksperiment 1 het 20 bokooie ($\bar{x}$ = 26.7 ± 0.96 kg) daagliks een van die volgende vier behandelings ontvang vir 45 dae: 2 ml mielie-olie (kontrole), of 1, 2, of 4 mg NMP in 2 ml mielie-olie/kg BW. In Eksperiment 2 het 75 bokooie ($\bar{x}$ = 32.1 ± 0.46 kg) daagliks een van die volgende vyf behandelings ontvang vir 45 dae: 2 ml mielie-olie (kontrole), 3 of 6 mg/kg BW NMP in 2 ml mielie-olie, 1 of 3 mg/kg BW T in fisiologiese soutoplossing. In albei eksperimente is behandelings binneaars toegedien. Paring het deur natuurlike dekking plaasgevind na aanvang van die behandelings. Nekaar-bloedmonsters is weekliks geneem, verwerk om serum te lewer, en serumprogesteroon(P4)-konsentrasies is deur radioïmmunobepaling (RIB) vasgestel. In Eksperiment 1 is geen reaksie op die toegediende dosis waargeneem nie, maar P4-konsentrasies het afgeneem (P = 0.03) in die behandelde diere. In Eksperiment 2 is geen reaksie op die toegediende dosis waargeneem nie, maar P4-konsentrasies in die NMP-behandelde diere (3.87 ± 0.618) was laer (P = 0.05) as in die kontrole (5.65 ± 747) of T-behandelde diere (4.73 ± 0.528, P = 0.08). Geen verskil in P4-konsentrasies is waargeneem tussen die T-behandelde en kontrole-diere nie (P = 0.59). Minder NMP-behandelde bokooie het dragtig geraak (59%) as kontrole- (77%) en T-behandelde bokooie (88%) (P = 0.053). Die resultate dui aan dat eksogene fenolamiene varieer in hul effek op die voortplantingprestasie van bokooie.

Keywords: Acacia, Angora goats, *N*-methyl-β-phenethylamine, pregnancy, progesterone, tyramine.

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Introduction

South Texas rangelands are dominated by a wide variety of shrubs, many of which contain secondary chemical compounds including the sympathomimetic amines *N*-methyl-β-phenethylamine (NMP) and tyramine (T) (Camp & Lyman, 1956; Camp & Moore, 1960; Camp *et al.*, 1964; Smith, 1977; Evans *et al.*, 1979). Such exogenous sympathomimetic amines act indirectly on animals by releasing biogenic amines (e.g. epinephrine, norepinephrine, dopamine) from tissue stores. Biogenic amines have been shown to suppress LH release in ewes (Deaver & Dailey, 1982), and heifers (Hardin & Randel, 1983) given exogenous GnRH, and to alter progesterone production by bovine corpora lutea *in vitro* (Rhodes & Randel, 1982). More recently, Donnelly & Dailey (1991) reported that dopamine depressed GnRH-induced LH release in sheep, whereas norepinephrine or serotonin did not. Since initiation of oestrous cycles in the postpartum cow (Short *et al.*, 1990) and in the seasonal breeding sheep and goat (Thiery & Martin, 1991) is marked by the resumption of GnRH secretion followed by pulsatile secretion of LH, factors that prevent or reduce GnRH or pulsatile LH secretion may cause infertility (Randel, 1990; Short *et al.*, 1990). The combination of poor reproductive performance (0% calf crop) observed in a group of Brahman–Hereford cattle in south Texas in 1988, and the observation

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that the animals were consuming 60–80% of their diet as *Acacia berlandieri* (Guajillo) during the 75-day breeding season (J.W. Holloway, 1989, personal communication), led to the hypothesis that exogenous phenolic amines, such as those known to occur in *Acacia berlandieri*, interfere with reproductive processes of ruminants.

Two experiments were conducted to investigate the effects of different levels of NMP and T treatment on progesterone production and pregnancy, using Angora goats as a model species, in order to determine if naturally occurring exogenous amines interfere with reproductive processes. Angora goats, being approximately a twentieth of the size of Braford cattle, were used in the studies to reduce the quantities of the compounds used. A lack of response to treatment by injection of NMP or T would suggest that these compounds were of little biological or economic importance, especially since any response would likely be further reduced if the compounds had first to be ingested. A negative response, however, would necessitate further, more intensive studies to elucidate more precisely the mode of action of the compound(s).

Materials and Methods

Experiment 1

Twenty mature Angora nannies ($\bar{x}$ = 26.7 ± 0.96 kg) were allotted by weight to one of four treatment groups of five animals, in the fall of 1989. Treatments consisted of daily i.v. injection of either 2 ml corn oil (control), or 1, 2 or 4 mg/kg BW NMP in 2 ml corn oil (NMP1, NMP2, and NMP4, respectively) for 45 days. The dose rates were based on estimates of the potential intake of NMP by free-ranging goats using the data of Camp & Moore (1960). Animals were weighed daily and the dose given was calculated from the previous day's weight. NMP and tyramine were obtained from Sigma Chemical Company, P.O. Box 14508, St Louis, MO USA. To have all nannies oestrous cyclic before treatment, an Angora wether injected with testosterone (500 mg in two doses) was allowed access to the nannies from September 15 until treatment was begun on October 10. On October 10 the teaser male was replaced by an intact male which remained with the nannies for the 45 days of treatment. Both the teaser and the intact male were fitted with marking harnesses, and the nannies were checked twice daily for signs of oestrus. The animals were maintained in a single group supplied with *ad libitum* Coastal Bermudagrass hay, minerals and water, supplemented with approximately 500 g/head/d 20% protein commercial goat pellets. Pregnancy was detected by ultrasound after 60 days and confirmed at parturition.

Experiment 2

A second experiment, based on the results of Experiment 1 and on additional data obtained from plant analyses (Forbes *et al.*, 1991), was conducted in October and November 1990. These data showed that tyramine was present in relatively large quantities (approximately 4 mg/g DM) in *Acacia berlandieri* forage. A total of 75 mature Angora nannies ($\bar{x}$ = 32.1 ±0.46 kg) were randomly allocated within body weight to one of five treatment groups of 15 animals. None of these animals had been previously used in experiments. Treatments initially consisted of a daily i.v. injection of either a control dose of 2 ml corn oil, 3 mg/kg BW tyramine, 9 mg/kg BW tyramine, 3 mg/kg BW NMP or 9 mg/kg BW NMP, but these rates were reduced after the first day of the trial (see **Results and Discussion**). Doses for individual animals were based on body-weight measured weekly. Tyramine was dissolved in physiological saline and NMP was dosed in 2 ml of corn oil as NMP was immiscible in saline. Five days after initiation of treatment, two intact male goats were placed with the nannies, and mating was by natural service, lasting throughout the 45-day treatment period. As in Experiment 1, the males were fitted with marking harnesses and nannies were checked daily for signs of oestrus. The animals were managed and fed as described in Experiment 1. Pregnancy was detected by ultrasound after 60 days and confirmed after 90 days.

Blood sampling and hormonal assays

In both experiments, prior to treatment and once a week thereafter for six weeks, 20 ml of blood were collected by jugular venepuncture from each nanny, processed to yield serum, and serum progesterone (P4) was quantified using validated RIA procedures (Williams, 1989). Intra- and inter-assay coefficients of variation were 10.8% and 13.7%, respectively.

Statistical analysis

Data were analysed to detect treatment effects on; (i) serum P4 concentration during the mid-luteal phase following the first observed oestrus; (ii) serum P4 production over time as determined by averaging P4 concentration across the sampling dates following each animal's first oestrus. Data were analysed using the GLM procedure of SAS (1988). Comparisons between least squares means were made using the PDIFF option. In Experiment 2, differences in the number of animals that became pregnant between control and treatment groups, both after the first oestrus and over the course of the study, were tested by chi-square tests of independence (Steel & Torrie, 1960). Where appropriate, actual values of probability (P) are given.

Results

Experiment 1

Despite the use of a teaser male, more than half of the nannies (12/20) did not begin to experience oestrous cycles until after the start of treatment and the replacement of the teaser with the intact male. Only these animals were, therefore, used in analyses. There was no evidence of a dose-response effect among the treated animals, and therefore they were analysed as one group. Because the blood samples were taken on a weekly basis, it was not possible to pin-point the mid-luteal phase precisely, thus the time at which blood samples were taken that defined the mid-luteal phase ranged from 6 to 7 days after oestrus in the control animals (x = 6.8 ± 0.20 days) and 6 to 10 days after oestrus in the NMP-treated nannies (x = 7.4 ± 0.48 days). The effect of treatment on serum P4 concentration during the mid-luteal phase was significant (control 9.9 ± 1.13 vs. NMP-treated 5.3 ± 0.96 ng P4/ml, P = 0.01) (Table 1). Similarly, serum P4 concentration, averaged over the five sample dates for which data were available on all animals, was higher (9.4 ± 0.62 vs. 6.2 ± 0.52 ng P4/ml, P = 0.0001) in the control group (n = 5) compared to the treated

animals (n = 7) (Table 1). All of the five control animals and five of the seven treated animals became pregnant at the first oestrus. Animals gained weight over the course of the experiment, the increase being significant ($P = 0.0001$) (Table 2).

Table 1 Serum P4 concentrations in the mid-luteal phase after first oestrus, and over all sampling dates, and numbers of animals which became pregnant after first oestrus and overall in Experiment 2

	n	P4 (ng/ml)	*SE*	
Experiment 1				
1st Oestrus				
Control	5	9.9	1.13	
Treated	7	5.3	0.96	
Overall				
Control	5	9.4	0.62	
Treated	7	6.2	0.52	
Experiment 2				
1st Oestrus				
Control	13	5.6	0.75	
Tyramine	27	4.7	0.53	
NMP	19	3.9	0.62	
Overall				
Control	13	4.5	0.39	
Tyramine	27	4.6	0.27	
NMP	19	3.4	0.32	
	n	Pregnant	Open	
Pregnant at 1st oestrus				
Control	13	9	4	
Tyramine	27	19	8	$P = 0.43$
NMP	19	10	8	
Pregnant overall				
Control	13	10	3	
Tyramine	27	24	3	$P = 0.05$
NMP	22	13	9	

Table 2 Initial and final weights of nannies in Experiments 1 and 2

	Initial weight (kg)	Final weight (kg)
Experiment 1		
Control	23.1 ± 2.10	29.2 ± 2.31
NMP	22.0 ± 1.78	27.1 ± 1.95
Experiment 2		
Control	31.5 ± 1.05	34.1 ± 1.23
Tyramine	32.2 ± 0.74	35.2 ± 0.87
NMP	32.0 ± 0.77	33.0 ± 0.91

Experiment 2

On the first day of treatment, two of the first three animals given the 9 mg T/kg BW tyramine treatment died very shortly after dosing. The surviving animal was removed from further treatment, and the remaining animals in the group were subsequently treated with 1 mg T/kg BW (T1). No other animals in either T-treated group showed further signs of distress during the remainder of the trial. Some animals in the 9 mg NMP/kg BW-treated group showed signs of incoordination of gait on the third day of treatment and the dosage for all animals in that group was reduced to 6 mg NMP/kg BW (NMP6). Of the NMP-treated animals, three animals in the NMP6 group and one animal in the 3 mg NMP/kg BW (NMP3) group died while being injected, while one animal in the NMP6 group was removed from treatment after showing signs of ataxia. This animal subsequently recovered fully and became pregnant, but was not included in any analyses. A single control animal died during the study. All of the animals which died had previously been in apparent good health. One animal in each of the control, NMP3 and NMP6 groups was small, and of low body weight. These nannies did not appear to have functional corpora lutea, based on P4 concentrations and the absence of breeding marks, and were therefore not included in any analyses. The data from one animal in the NMP3 group were deleted from the serum P4 analysis when examination of the data suggested that a silent oestrus occurred. In addition, two animals in the NMP3 group and one animal in the NMP6 group did not experience oestrus and did not breed, and their data were therefore excluded from P4 analyses. In all, data from 13 control nannies, 12 T1, 15 T3, 10 NMP3, and 9 NMP6 nannies were used in statistical analyses of serum P4 concentration and pregnancy resulting from breeding at first oestrus. For the determination of effects of treatment on pregnancy over the entire trial, the data from the three NMP-treated animals which showed signs of oestrus, but did not become pregnant, were included. No differences ($P = 0.20$) were detected between level of dosing within treatment group in P4 concentration either in the first mid-luteal phase or in the average concentration over the course of the study, or in the number of animals that became pregnant, so treatment groups within compounds were combined before further analysis. As in Experiment 1, blood samples which defined the mid-luteal phase were collected over a narrow range of days being 8 and 11 days after oestrus for control and T-treated nannies ($x = 9.5 \pm 0.22$ and 9.2 ± 0.16, respectively), and 7 to 10 days ($x = 9.0 \pm 0.25$) for NMP-treated nannies. NMP treatment reduced P4 concentrations during the mid-luteal phase following the first oestrus after the initiation of treatments compared to the controls ($P = 0.05$) and T-treated nannies ($P = 0.08$). The difference in P4 concentration between control and T-treated nannies was not significant ($P = 0.58$) (Table 1). Similarly, the data show that P4 concentrations, averaged over the three sampling dates following first oestrus, were reduced by treatment with NMP compared with control ($P = 0.02$) or T-treated animals ($P = 0.005$) (Table 1), but that tyramine treatment did not reduce serum P4 concentration ($P = 0.51$). Animals which became pregnant at the first oestrus were not reduced by treatment ($P = 0.43$), but overall NMP treatment reduced ($P = 0.05$) the numbers of nannies that became pregnant (13/22) compared with control (10/13) and tyramine-treated nannies (24/27) (Table 1). All animals gained or maintained weight over the course of the study, with the NMP-treated animals increasing in weight the least

(Table 2). The increase in weight across groups from initial to final weight was significant ($P = 0.006$)

Discussion

The dose levels used in these studies reflected our understanding of the quantities of the amines likely to be consumed, and likely to be degraded in the rumen, based on our own work, that of Camp & Moore (1960), and Camp (1970). Camp *et al.* (1964) reported the LD_{50} for rats injected intraperitoneally with NMP to be 200–225 mg/kg BW, and Flournoy *et al.* (1970) administered a total of 1620 mg NMP, by i.v. injection, to a 30 kg BW Spanish goat over a 130-min period without apparent lethal effects. Additionally, Camp (1970) reported injecting rats with 25 mg NMP/kg BW intraperitoneally, daily for two weeks without ill effects. Little data was available for LD_{50} values for tyramine-treated animals. Material safety data sheets supplied with the tyramine indicated that the LD_{50} for mice and rabbits injected intravenously was 300 mg/kg BW. By using these figures, single daily i.v. injections of 3 and 9 mg/kg BW were proposed in an attempt to achieve a dose response. The deaths of animals in Trial 2 may reflect variation between animals in their ability to handle the stress induced by the administration of the compounds intravenously, or may have been a consequence of using corn oil as a carrier for the NMP. However, all 25 nannies were dosed with corn oil in Experiment 1 and none of them died. In addition, subsequent investigations using the hydrochloride salt of NMP, without oil as a carrier, at a dose level of 4 mg NMP/kg BW resulted in the death of an animal showing identical, shock-like symptoms (Forbes *et al.*, unpublished data).

The results provide *in vivo* support for the findings of Rhodes & Randel (1982), who showed that *in vitro* P4 production by bovine corpora lutea was depressed when luteal cells were treated with epinephrine, norepinephrine or dopamine. In both experiments, NMP dosed intravenously at levels above 1 mg/kg BW reduced both serum P4 concentrations and the percentage of animals that became pregnant. In contrast, tyramine, though being toxic to some animals at levels of 9 mg/kg BW, had no apparent effect on serum P4 concentration or on subsequent conception. In spite of the reported appetite-depressing effects of similar amines such as amphetamine, neither compound appeared to induce lasting effects on appetite or feed intake as indicated by weight changes from the beginning to the end of the trial (Table 2).

These results show that at least one of the exogenous amines has the potential to reduce reproductive performance in Angora goats if introduced into the bloodstream in single pulses in quantities greater than 1 mg/kg BW. Goats are largely browsers and are thus normally exposed to a greater array and greater concentrations of allelochemicals than cattle, which evolved as grazers. Allelochemicals, though present in the family Gramineae, are certainly less common and are seldom accumulated in quantity (Harborne, 1988). Consequently, goats may be expected to have evolved more efficient and complete mechanisms for detoxifying allelochemicals than cattle. Cattle are likely, therefore, to be more susceptible to NMP than goats. There is evidence that animals which utilize browse as their main source of feed have larger livers, and have larger salivary glands than grazers (Hofmann, 1989). Some browsers produce large quantities of proline-rich saliva which preferentially bind tannins; a mechanism not utilized by cattle or sheep (Austin *et al.*, 1989). Cattle which consume large amounts of browse may be exposed to potentially toxic quantities of allelochemicals. Similar interspecific variability in reaction to plant secondary chemicals has been shown in the studies on pine needle abortion, where cattle are much more susceptible than sheep (James *et al.*, 1989).

Despite the studies carried out on rats (Barraclough & Wise, 1982; Champney *et al.*, 1986; Slikker *et al.*, 1986; Yeh *et al.*, 1986), there is a paucity of information concerning the impact of exogenous, physiologically active, plant compounds on reproduction in any livestock species, and further research is needed on the mechanisms of allelochemical toxicity, on the ability of livestock to detoxify β-phenethylamines, and to determine the location(s) of detoxification. While the metabolic function of many of these allelochemicals is not understood, they may have considerable importance in preventing both insect and mammalian herbivory (Bryant *et al.*, 1989; Harley & Thorsteinson, 1967). The possibility also remains that the progesterone suppressing activity of exogenous amines such as NMP may be mediated through mechanisms other than direct effects on the corpus luteum. While these experiments cannot indicate the mechanisms by which progesterone production was suppressed by NMP, two possible mechanisms may be postulated. Firstly, the work by Deaver & Dailey (1982) and by Hardin & Randel (1983) indicates that catecholamines can suppress pituitary secretion of luteinizing hormone (LH). Depressed levels of pituitary LH production could, in turn, lead to a reduction in plasma progesterone concentration. Secondly, results from other studies (Wagner *et al.*, 1972; Li & Wagner, 1983) indicate that ACTH challenge can reduce plasma progesterone concentrations. Studies by the senior author and co-workers (Carpenter *et al.*, 1992; 1993) indicate that NMP increases plasma norepinephrine and cortisol concentrations and decreases GnRH stimulated plasma LH concentrations, while having little effect on plasma ACTH concentrations. Thus it appears likely that NMP interferes indirectly with progesterone production through its affects on adrenal release of cortisol and/or norepinephrine.

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