Dopamine Antagonist Speeds Up Tail Regeneration in Lizards Exposed to Continuous Darkness: Evidence for Prolactin Involvement (42969)

PATRICK I. NDUKUBA AND A. V. RAMACHANDRAN

Division of Developmental Physiology and Endocrinology, Department of Zoology, M. S. University of Baroda, Baroda-390002, Gujarat State, India

Abstract. **In earlier studies, we demonstrated that continuous light (LL:LD, 24:0) stimulated tail regeneration wheras continuous darkness (DD:LD, 0:24) and pinealectomy depressed the same in the Gekkonid lizard, *Hemidactylus flaviviridis*, and, furthermore, exogenous prolactin significantly enhanced the regeneration process in lizards kept in 0:24 LD. However, the regeneration process in animals exposed to 24:0 LD was unaffected by the dopamine agonist, bromocriptine. This study with pimozide, an antipsychotic drug, and a potent dopamine receptor antagonist was conducted to ascertain whether the dopaminergic regulation of prolactin release is operative in lizards, as in mammals, and to provide further evidence for prolactin involvement in regenerative growth. Once daily intraperitoneal injection of 50 μg/kg pimozide to *H. flaviviridis*, 5 days prior to tail autotomy and 50 days thereafter, stimulated the regeneration process in lizards exposed to 0:24 LD. The initiation of regeneration, the total length of new growth (regenerate) produced by Day 50, and the total percentage replacement of the lost (autotomized) tails at the end of 50 days of experimentation were all significantly enhanced in pimozide-treated animals as compared with their counterparts injected with 0.6% sterile saline; in fact, better than saline-injected controls exposed to 24:0 LD of 638 lux intensity. The daily growth rate was also enhanced in pimozide-treated lizards. Interestingly, the pattern of regeneration as well as the final regenerate of pimozide-treated lizards were similar to those observed earlier in ovine prolactin-treated animals exposed to similar experimental photoperiodic schedules. The operation of the dopaminergic regulatory mechanism of prolactin release in lizards, as in mammals, is strongly indicated and the involvement of prolactin and its regulation by photoperiodism during lacertilian tail regeneration are discussed.** [P.S.E.B.M. 1989, Vol 192]

Prolactin (PRL) has been reported to have numerous activities in vertebrates including effects on osmoregulation, growth and development, and reproduction. However, the predominant osmoregulatory role played by PRL in fishes has prompted Nicoll (1) to suggest that this action may have been the original vertebrate PRL regulatory function. In addition, he has proposed that PRL may have comparable osmoregulatory importance during the ontogeny of higher vertebrate groups. PRL has been established as a growth promoter in developing organisms (2) and in regenerating systems (3, 4) and has been shown to stimulate protein synthesis in developing tadpoles (5). It has been demonstrated that the plasma concentration of PRL is highest during the light period of the circadian cycle (6). Indeed, it has been shown that serum levels of PRL are affected by the length of light and photoperiodic cycle. Long light periods elevate serum PRL levels whereas shorter lengths produce lower levels (7). Previous studies with the lizards, *Anolis carolinensis* (8) and *Hemidactylus flaviviridis* (9) demonstrated that long length photoperiod speeds up the rate of tail regeneration whereas a short light period slows down the rate. Similar results were obtained in the newt, *Notophthalmus viridescens* forelimb regeneration using either continuous light or total darkness (10).

Neuroendocrine studies using neuropharmacologic agents have amply demonstrated that dopamine has an inhibitory role in the control of PRL release. Studies with catecholamine synthesis inhibitors have unequiv-

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ocally demonstrated that a catecholamine is involved in the inhibitory control of PRL release (cf. 11). It is well documented that dopamine is the main regulator of pituitary PRL secretion and that it exerts its effects directly at the level of the lactotroph (12). Dopamine is known to modulate the light-evoked responses of horizontal cells in fish (13), turtle (14), and Xenopus (15) retinas. Dopamine receptor stimulation inhibits inositol phosphate production (16) and its neurons inhibit gene transcription for neuropeptides in rat (17).

Noradrenaline is also involved in the control of PRL secretion, acting at the level of the hypothalamus (18). The presence of both dopamine and noradrenaline in an anterior pituitary gland transplanted under the kidney capsule has been reported (19, 20). Moreover, results obtained in grafted rats treated chronically with dopamine agonists or antagonists (21) suggested the existence of catecholaminergic regulatory mechanisms of PRL secretion from the ectopic pituitary gland.

The catecholamine antagonists block the action of the catecholamine on its receptor. The antipsychotic drugs were a good source of catecholamine receptor blockers because among most antipsychotic drugs a positive correlation between dopamine receptor-blocking ability and antipsychotic potency exists (11). Table I (cf. 11) summarizes the studies performed with the receptor-blocking drugs. Of this group of drugs, only pimozide is known to be a specific blocker of dopamine receptors over a limited dose range (22). Although all of the drugs listed appear to implicate some monoamine as being involved in the inhibitory control of PRL secretion, only the studies with pimozide clearly focus on dopamine as a monoamine that is involved in inhibiting PRL release (22).

Judging from the numerous studies cited above, an increasing number of reports have appeared in literature in which the PRL and photoperiod were implicated in various physiologic and endocrine processes in vertebrates and as growth promoters in regenerating systems. However, to our knowledge, no investigation has attempted the use of a pharmacologic agent(s) to identify the mechanism of PRL release during lacertilian tail regeneration. Previous experimental evidence suggests that the injection of drugs that increase brain serotonin (5-HT) stimulates the release of pituitary PRL in avian species (23–25) or intracerebroventricular injection of the neurotransmitter (26). Parachlorophenylalanine (*p*-CPA), as well as other 5-HT antagonists, has been shown to decrease basal PRL levels when administered systemically to male chickens (27), whereas quipazine maleate produces the opposite effect (27). Quipazine maleate is a known 5-HT agonist (26), but unlike 5-HT, it can easily cross the blood-brain barrier and is not metabolized by monoamine oxidase. *p*-CPA is reported to deplete the 5-HT stores in the brain, peripheral tissues, and blood in rats and dogs (28) and the drug acts by reducing a serotonergic stimulation of PRL release in teleosts (29). Thus, indirect evidence, from studies with 5-HT agonists and antagonists, indicates that 5-HT has a stimulatory role in the regulation of PRL secretion in teleosts, birds, and mammals. There are no comparable reports in reptilian species (30) and our varied efforts, in this and other similar studies, are directed toward the establishment of the Gekkonid lizard as a model for the study of the mechanism of PRL release in reptiles. Hence, this report demonstrates the enhancement of tail regeneration in the lizard, *H. flaviviridis* exposed to continuous darkness, with daily intraperitoneal injection of the antipsychotic drug, pimozide, a potent dopamine receptor blocker, possibly occurring by increased PRL release via the dopaminergic mechanism.

Materials and Methods

Experimental Animals. Adult *H. flaviviridis* of both sexes weighing 10 ± 1 g and measuring 80 ± 5 mm snout to vent length were obtained from a commercial supplier (M/s. Zoophyton, Baroda, India) and

Table I. Effect of Catecholamine Receptor-blocking Drugs on Prolactin Secretion (cf. 11)

Drug	Receptors blocked	Effect on Prolactin Secretion	Reference
Chloropromazine	Dopamine Norepinephrine Histamine 1	Increase	Lu *et al.*, 1970 Kleinberg *et al.*, 1971
Perphenazine	Dopamine Norepinephrine Histamine 1	Increase	Ben-David *et al.*, 1970 MacLeod *et al.*, 1970 Ben-David *et al.*, 1971
Haloperidol	Dopamine Norepinephrine	Increase	Dickerman *et al.*, 1972
Cyproheptadine	Dopamine Serotonin	Increase	Clemens, unpublished data
Promethazine	Histamine 1	Decrease	Clemens *et al.*, 1974
Pimozide[a]	Dopamine	Increase	Clemens *et al.*, 1974
Sulpiride	Dopamine	Increase	Clemens *et al.*, 1974

[a] Highly potent.

maintained *ad libitum* on a diet of cockroaches for a period of 7 days for acclimation to the laboratory conditions. A total of 30 lizards was used for this investigation, and they were balanced for size and sex in order to eliminate any possible error in the final statistical analysis due to size and sex differences. The animals were divided into three groups and exposed to 0:24 LD photoregime.

Group 1: pimozide treated (50 μg/kg body wt). The first group of 10 lizards received once daily an intraperitoneal injection of 50 μg/kg pimozide 5 days prior to tail autotomy and 50 days thereafter.

Group 2: control lizards (0.6% sterile saline). The second group of 10 lizards, which served as the control, received once daily an intraperitoneal injection of 0.6% sterile saline 5 days prior to tail autotomy and 50 days postcaudal autotomy.

Group 3: control lizards (without saline). A third group of 10 animals, which served as the second control, proceeded as in Group 2 but without a daily saline injection.

Preparation of Pimozide (50 μg/kg). Pimozide (orap by Ethnor Ltd., Bombay, India) was prepared and stored in a refrigerator at 4°C for daily use. The drug was dissolved in a few drops of ethanol and then made up to the required concentration with warmed (40°C) sterile saline (0.6%). All animals in this group received a daily intraperitoneal injection of 0.1 ml of the prepared solution, giving an approximate daily dose of 0.5 μg/animal.

Preparation of Saline (0.6%). A total of 0.6 g of reagent grade sodium chloride (NaCl) was dissolved in 100 ml of redistilled water with a dew drops of ethanol and stored in a refrigerator for daily use.

Experimental Set Up. Tail autotomy was performed by pinching off the tail at the third segment from the vent. The length of tail removed from the animals varied from 50 to 60 mm depending on the length of each tail from the third segment to the tip of the tail. The animals were exposed to 0:24 LD and administered once daily an intraperitoneal injection of 50 μg/kg pimozide and 0.6% sterile saline, in the case of the control group, for a period of 50 days after tail autotomy. Food and water were provided *ad libitum* throughout the entire period of experimentation. Except for a period of about 3 min of daily exposure to dim red light for taking measurements and giving injections, all of the animals were completely deprived of light. The investigation was conducted during the months of September and October and the average daily temperature at the level of the animals was 25°C.

Statistical Analysis. The length of new growth (regenerate) was measured and recorded daily with a measuring rule graduated in millimeters and the recorded measurements at fixed time intervals of 10, 20, 30, 40, and 50 days postcaudal autotomy were later used for morphometric calculations. The data on the length of tail regenerated and total percentage replacement were subjected to Student's t test for statistical significance between pimozide-treated and nonsaline/saline-injected animals. Values which were different at the $P < 0.05$ level were considered statistically significant.

Results

The results are clearly shown in Table II and Figures 1–3. As there was no statistically significant difference between lizards with and without saline injection, we have opted to represent, for graphical purposes, only the saline-injected controls.

Growth Rate, Total Length of Tail Regenerated, and Total Percentage Replacement. The regeneration blastema appeared in pimozide-treated lizards exposed to 0:24 LD (Group 1) by Days 8–10 and in their counterparts injected with sterile saline (Group 2) and those without saline (Group 3) by Days 12–14 postcaudal autotomy. The total length of tail regenerated by the 50th day in intact animals injected with 50 μg/kg pimozide once daily was 36.9 mm and those given once daily an intraperitoneal injection of 0.6% sterile saline and those without saline were 26.3 and 26.8 mm which corresponded to a replacement of 68.8%, 49.6%, and 50.1%, respectively (Figs. 1 and 3). The pattern of growth rate (Fig. 2) indicates a linear increase peaking at 30–40 days in pimozide- and saline-treated lizards. Comparisons between the three groups of animals (Student's t test) revealed statistical significance between pimozide-treated lizards on the one and saline/nonsaline-treated animals on the other at the 5% level.

The arbitrary stages of tail regeneration shown in Table II can be described as follows: (i) wound healing—when the cut surface of the tail stump is com-

Table II. Approximate Number of Days Taken to Reach the Various Arbitrary Stages of Tail Regeneration in Pimozide-treated and Control Lizards, *H. flaviviridis*, Exposed to Continuous Darkness during the Monsoon Months of September and October

Experimental animals	Wound healing	Blastema	Early differentiation	Mid-differentiation	Late differentiation	Growth
Pimozide-treated	5	8–10	12–14	20	30	40[a]
Saline-treated (control)	7	12–14	18–20	25	35	45

[a] Days postcaudal autotomy.

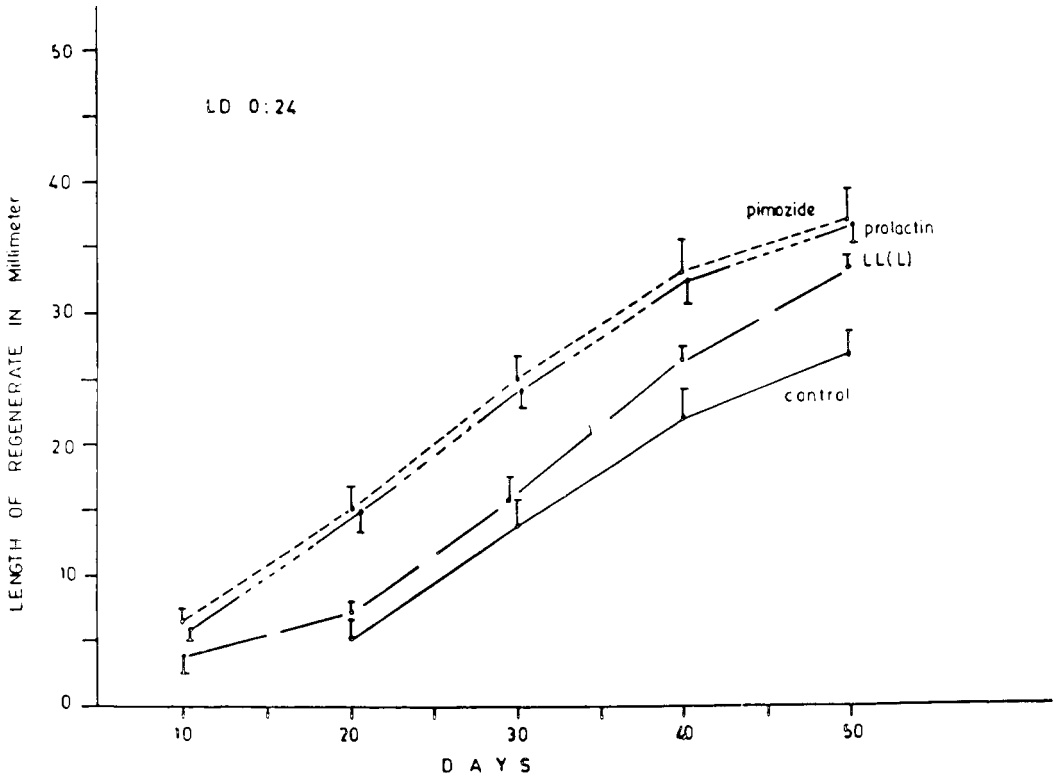

Figure 1. Length of tail regenerated in control and pimozide-treated *H. flaviridis* exposed to continuous darkness (0:24 LD). Vertical bars represent ±SD. Prolactin and LL(L) continuous light of low intensity (638 lux). Data from Ndukuba and Ramachandran (9, 30).

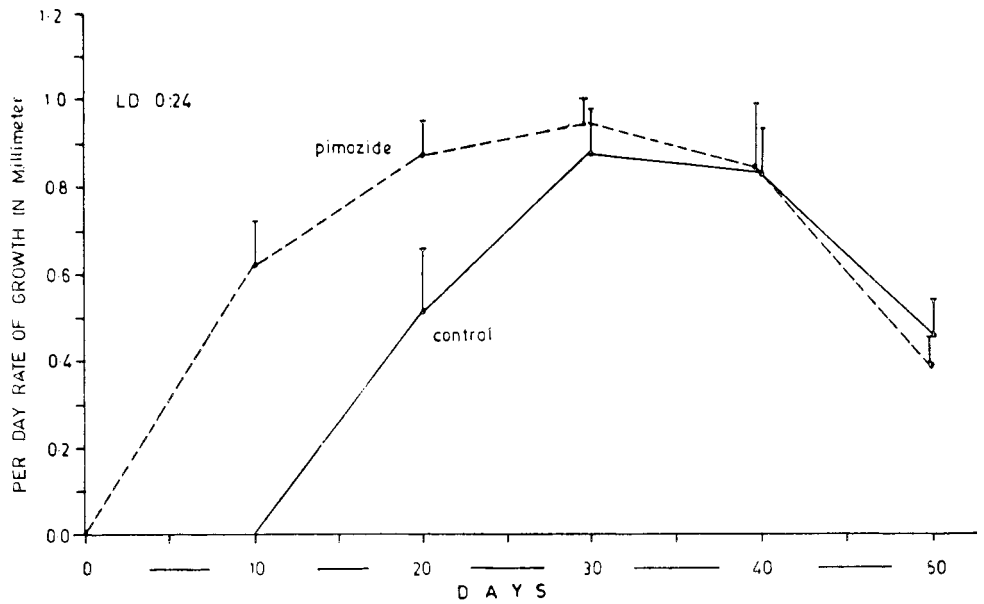

Figure 2. Per day rate of growth in control and pimozide-treated *H. flaviridis* exposed to continuous darkness (0:24 LD). Vertical bars represent ±SD.

pletely covered by an epithelium; (ii) blastema—a conical outgrowth from the tail stump which contains the primordial cells of the regenerate; (iii) early differentiation—a small elongation from the blastema; (iv) mid-differentiation—the regenerate tapers slightly from the blastema cone; (v) late differentiation—the tapering of the regenerate becomes pronounced; and (vi) growth—the regenerate begins to take the form of a functional organ, resembling the lost tail (for a detailed description and references, see 31).

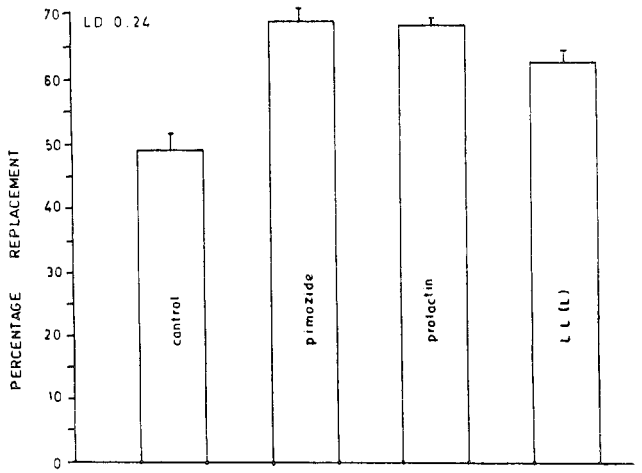

Figure 3. Percentage of tail replaced in control and pimozide-treated *H. flavivirdis* exposed to continuous darkness (0:24 LD). Vertical bars represent ±SD. Protaction and LL(L) continuous light of low intensity (638 lux). Data from Ndukuba and Ramachandran (9, 30).

Discussion

The results of this investigation demonstrate that the antipsychotic drug pimozide, a potent dopamine receptor antagonist, stimulated tail regeneration in the Gekkonid lizard, *H. flaviviridis* maintained in the 0:24 LD photoregime. The initiation of regeneration, the total length of new growth (regenerate) produced by Day 50, and the total percentage replacement of the lost (autotomized) tails by the 50th day were all significantly enhanced in pimozide-treated animals when compared with those of their saline-injected counterparts; in fact, better than saline-treated lizards exposed to 24:0 LD of 638 lux intensity (see Figs. 1 and 3, cf. 9). The growth rate (Fig. 2) was enhanced during the early stages of tail regeneration (blastema and early differentiation) in pimozide-treated animals which accounted for the total better regenerative performance in this group of lizards.

PRL secretion is known to be under the tonic inhibitory control of the central nervous system. Suppression of this inhibitory influence, by lesions in the median eminence of the hypothalamus (32), transplantation of the pituitary gland under the kidney capsule (33), or transection of the pituitary stalk (34) results in increased PRL secretion. Depletion of hypothalamic catecholamines by compounds which inhibit their synthesis resulted in a rise in serum PRL (35). In contrast, pharmacologic procedures which enhance the amine levels in brain either by the injection of monoamine oxidase inhibitors or L-dopa inhibit PRL release (35, 36). It is generally accepted that inhibition of anterior pituitary PRL secretion is regulated mainly by dopamine (DA) released from median eminence terminals. The presence of DA in hypophysial portal blood (37) and the localization of DA receptor sites in the anterior pituitary gland (38) suggest that DA could act on membrane receptors in hypophysial anterior lobe. However, the presence of intracellular DA in the anterior pituitary gland (39) and the demonstration that its variations are inversely related to serum PRL (40) suggest a second level of DA action. The observation that an increase in circulating PRL is associated with a decrease in DA content in the pituitary gland and vice versa (40) suggested that DA could be contained in the lactotroph cells. Other authors (41) reported that DA and PRL were present in the same particle. The study of Gallardo *et al.* (42) presents direct evidence of the accuracy of both contentions.

The present study is the first investigation which demonstrates the effect of the antipsychotic drug and a potent dopamine antagonist on tail regeneration in a tropical saurian. In previous reports, we have shown that continuous light stimulates tail regeneration whereas continuous darkness depresses the same in the lizard, *H. flaviviridis* (9) and, furthermore, the lateral eyes, or retinas, do not participate in photoperiodically significant photoreception since blinded lizards regenerate their lost (autotomized) tails like their sighted counterparts exposed to similar experimental photoperiodic schedules (43). Moreover, it has been demonstrated that the pineal organ is the principal site of extraretinal photoreception in *Hemidactylus* since both pinealectomy and light deprivation to the pineal abolished the stimulatory influence of increasing lengths of light and significantly retarded the regeneration process (44) and exogenous PRL stimulated tail regeneration in intact but not pinealectomized lizards exposed to continuous darkness, suggested that the pineal is somehow linked with the favorable influence of light on tail regeneration in lacertilians (4). In our recent investigations, *p*-CPA, an inhibitor of tryptophan hydroxylase (45, 46) and an agent employed for chemical pinealectomy, retarded tail regeneration in animals exposed to 24:0 LD, indicating that lizards with physically intact pineals but deprived of their ability to synthesize 5-HT do not exhibit the favorable influences of light on tail regeneration in lizards (47). However, bromocriptine, a potent DA agonist, did not affect the regeneration process in lizards exposed to either 24:0 LD or 0:24 LD photoregimes (30).

Since bromocriptine failed to retard tail regeneration, it was thought pertinent to investigate with the potent DA receptor blocker, pimozide. Once daily intraperitoneal injection of pimozide (50 μg/kg) for 50 days postcaudal autotomy enhanced the regenerative performance of lizards maintained in 0:24 LD when compared with their saline-injected counterparts. Interestingly, the regenerative performance of pimozide-treated animals was similar to that of exogenous ovine PRL-treated lizards (4). These results may suggest that in lizards, as in mammals, the antipsychotic drug, pimozide, has the potency of blocking the inhibitory role of DA on PRL release. Several indications infer that

hypothalamic neurons which secrete prolactin-inhibiting factor (PIF) are tonically stimulated by catecholaminergic fibers, thus maintaining, in resting condition, a sustained release of PIF and, as a consequence, PRL secretion is restrained (48). Suppression of the influence of catecholamines by pharmacologic procedures results in the enhancement of PRL release (48). There is considerable evidence in favor of regulation of PRL cells by DA and 5-HT in mammals (49) and, to a lesser extent, in other vertebrates (50). The drug *p*-CPA reduces 5-HT synthesis by inhibiting tryptophan hydroxylase and so blocking the conversion of tryptophan to 5-HT (44, 45). That *p*-CPA does act by reducing serotonergic stimulation of PRL is indicated by the reported decline in brain 5-HT and pituitary cAMP levels in *Salmo gairdneri* following *p*-CPA treatment (29). In addition, Olivereau (51) has reported that *p*-CPA produced a decrease in PRL cell function in *Anguilla anguilla*, as indicated by reduced cell nuclear area and increased cytoplasmic granulation. In some teleosts, DA seems to be inhibitory (52). The report of James and Wigham (53) suggests that DA exerts an inhibitory influence on PRL cells in *S. gairdneri*. The ability of domperidone to stimulate PRL synthesis in *S. gairdneri* suggests that the DA receptors controlling PRL secretion are situated in the pituitary since this drug is unable to cross the blood-brain barrier (54).

The earlier observation that bromocriptine had no effect on regenerating lizards exposed to either 24:0 LD or 0:24 LD (47), coupled with the present finding that pimozide-stimulated tail regeneration in 0:24 LD exposed animals, may suggest that both serotonergic and dopaminergic systems of PRL release are operative on par at the intermediate photoperiodic regime of 12:12 LD. With increasing photoperiodism, there is a direct antagonism by 5-HT of the dopaminergic system that inhibits PRL release. One possible mechanism is that 5-HT may inhibit DA (or PIF) release from the median eminence of the hypothalamus. Caligaris and Teleisnik (55) have suggested that such inhibition of DA neurons does occur and involves interneurons. In mammals, where the portal blood supply is the major functional link between the hypothalamus and the adenohypophysis (56), there is good evidence that 5-HT acts at the hypothalamus, rather than directly on the pituitary (49). In birds as in mammals, the secretion of anterior pituitary hormones is under the influence of the hypothalamus (57) and the avian hypothalamus appears to exert predominantly stimulatory influence on the release of pituitary PRL (58). Evidence exists that the activation of the turkey hypothalamus by electrical stimulation induces PRL release via serotonergic neurons within the ventromedial nucleus (59). It is, therefore, interesting to speculate on the possible similarity between mammals, birds, and lizards in the hypothalamo-hypophysial circulatory system. Another possible mechanism involves the release by 5-HT of a PRL-releasing factor (PRF) which then antagonizes the effect of DA (or PIF) at the pituitary level. The antagonistic effect of 5-HT (or PRF) on DA (or PIF) probably reaches the peak in the 24:0 LD condition with the serotonergic neurons fully activated. With decreasing photoperiodism, the dopaminergic mechanism becomes activated and a direct antagonism by DA of the serotonergic system that stimulates PRL release occurs. Alternatively, the release by DA or PIF antagonizes the effects of 5-HT or PRF at the level of the hypothalamus. This may attain its peak in the 0:24 LD photoperiodic schedule where the dopaminergic neurons are fully activated.

Viewed in this perspective, our observation that bromocriptine failed to influence tail regeneration in the 24:0 LD exposed animals indicates that the dopaminergic system does not function under this regimen since the antagonistic 5-HT/PRF mechanism of PRL release is functioning maximally. On the other hand, bromocriptine also did not affect the regeneration process in lizards maintained in the 0:24 LD schedule, probably because the DA/PIF mechanism is functioning maximally leading to the saturation of the dopaminergic receptors on lactotrophs and, consequently, the agonist has no available binding sites. However, pimozide stimulated tail regeneration in the 0:24 LD exposed lizards, confirming our proposition that the dopaminergic mechanism of PRL release may be operative under this condition. And having previously shown that *p*-CPA, an inhibitor of 5-HT synthesis, retarded tail regeneration in the 24:0 LD condition (49), we feel that it will be interesting to conclusively demonstrate the serotonergic mechanism of PRL release during lacertilian tail regeneration with the help of one of the well known 5-HT receptor antagonists, such as cyproheptadine, methysergide, or SQ10,631. This investigation is now in progress in our laboratory using methysergide, a potent 5-HT receptor antagonist. There is also an ongoing study in our laboratory in search of conclusive experimental evidence to support the dopaminergic regulatory mechanism, with bromocriptine injection in lizards exposed to 12:12 LD where we have suggested that both the serotonergic and dopaminergic mechanisms of PRL release are functioning on part (this report).

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