Hormonal Interaction in Amphibian Metamorphosis

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SYNOPSIS. The climactic stages of amphibian metamorphosis constitute a period characterized by radical morphological changes that are driven primarily by the thyroidal hormones. Radioimmunoassays show that levels of thyroid hormones (TH) rise to a peak during metamorphic climax. Accompanying peaks are reported for ACTH, adrenal corticoids (AC), insulin (I) and prolactin (PRL). AC enhance the metamorphic action of TH by increasing their binding to nuclei of target cells. TH, in turn, act to raise levels of AC by stimulating the differentiation of the median eminence thus facilitating the flow of a CRF from the hypothalamus to the adenohypophysis, by synergizing with ACTH and by stimulation of the interrenals through some other route. During the metamorphic period, at least as far as climax, PRL antagonizes TH, perhaps at the thyroidal level and certainly at the level of target cells. PRL may antagonize by inhibiting induction of hydrolytic enzymes by TH, by alteration of hydromineral responses or by altering levels of binding of TH to receptors. The antagonistic action of PRL is mimicked by cAMP. A surge of PRL that is released into the plasma during metamorphic climax seemingly produces no antagonistic effect on thyroidal actions.

THYROIDAL HORMONES

Among the various vertebrate species the thyroid gland performs many functions but none is more spectacular than its action in stimulating the transformation of an aquatic fish-like tadpole into a land-dwelling frog. The degree and extent of the changes that constitute metamorphosis vary significantly throughout the class Amphibia (see Dent, 1968; Houdry and Beaumont, 1985). It is, however, clear that those changes are regulated primarily by the hormones of the thyroid gland (Guderian, 1912, 1914; Smith, 1916; Hoskins and Hoskins, 1919): thyroxine (T₄) and triiodothyronine (T₃). Although T₃ has usually been found to be more effective, both thyroidal hormones (TH) compete for the same receptor sites on the nuclei of the liver in the tadpole (Galton, 1986).

Serum levels during metamorphosis

Through the years, a number of studies have been directed toward ascertaining the circulating levels of TH during premetamorphic and metamorphic stages of development. Etkin (1935) approached the problem indirectly by immersing young larvae (usually thyroidectomized) in various concentrations of T₄. He found that at very low levels (approximately 780 ng/ml) hind limb growth, representing the first of the anuran metamorphic changes, progressed, but that the degenerative changes of metamorphic climax required an increase by a factor of approximately 300. Later, chromatographic and densitometric analyses of T₄ (Race and Cameron, 1966) and protein bound iodide (Just, 1972), and radioimmunoassays (RIA) (LeLoup and Buscaglia, 1977; Miyauchi et al., 1977; Regard et al., 1978; Mondou and Kaltbach, 1979; Suzuki and Suzuki, 1981) carried out on pooled plasma of anuran larvae confirmed that TH levels are low until the early phases of metamorphosis, characterized by rapid and differential growth of the hind limbs (prometamorphosis), when TH levels ascend swiftly to a peak that occurs at, or just before, metamorphic climax. Following climax, levels fall precipitously and in postmetamorphic individuals are often extremely low. Since the cited investigations were carried out exclusively on tadpoles of the bullfrog, Rana catesbeiana, except for one (LeLoup and Buscaglia, 1977) on Xenopus laevis, and mostly on animals reared in the laboratory, a recent study (Weil, 1986) followed T₄ levels in unpoled...
blood of freshly collected larvae of a different frog, *Rana clamitans*. In those animals the levels of T₄ differed in that they were moderately high in premetamorphic stages, but they still peaked at climax. The pattern of variation in TH levels established in anuran larvae also appears to obtain basically for urodele larvae as shown for *Ambystoma gracile* (Eagleson and McKeown, 1978), *Ambystoma tigrinum* (Larras-Regard et al., 1981) and the plethodontid salamander, *Eurycea bislineata* (Alberch et al., 1986). Whenever non-pooled samples have been used, great individual variation has been noted (Mondou and Kaltenbach, 1979; Alberch et al., 1986; Weil, 1986). Several explanations for the variation, such as a pulsatile manner of secretion, have been suggested, but no clear understanding of the variation has yet been forthcoming.

**Hypothalamic control of metamorphosis**

The importance of the hypothalamus in the regulation of metamorphosis was demonstrated by Etkin in 1938, well before the role of the hypothalamic-pituitary portal system of hormone release had been established. He showed that a pituitary autograft in the tail of a tadpole of *Rana pipiens* permitted the growth of hind limbs through much of prometamorphosis but was incapable of providing sufficient thyroidal stimulus for the completion of metamorphic climax. Confirming observations were made by Uyematsu (1940) on larvae of *Bufo bufo*, by Hanoaka (1967) on larval *Rana pipiens*, and especially by Etkin and Sussman (1961) who in larvae of *Ambystoma maculatum* placed a plastic barrier in the median eminence (ME) to interrupt nervous and vascular connections between the hypothalamus and the pituitary. Metamorphosis was halted, except in some animals whose blood vessels reformed the hypothalamic-pituitary portal system. Those animals completed metamorphosis, demonstrating the need for a circulating, thyrotropic regulating or releasing factor and for a direct link between the pituitary and the hypothalamus.

The discovery and eventual synthesis of the mammalian thyrotropic releasing hormone (the tripeptide, pyro-Glu-His-Pro-HN₂, now known as TRH) by Guillimen and colleagues (see Vale et al., 1975), excited students of amphibian metamorphosis who were eager to test its effects on amphibian larvae. The results were largely disappointing. Enhancement of metamorphic changes in response to treatment with synthetic TRH was usually observed neither in anurans (Gona and Gona, 1974) nor in urodèles (Taurog et al., 1974; Darras and Kühn, 1983). Surprisingly, TRH was found to be abundant in amphibian brain and skin (Jackson and Reichlin, 1974). Although some thyrotropic regulating factor from the hypothalamus is essential to the completion of metamorphosis, a significant role for the tripeptide known as TRH would appear to be unlikely.

**Adrenocortical Steroids**

Beginning with that of Bock in 1938, several early studies (Frieden and Naile, 1955; Kaltenbach, 1958; Kobayashi, 1958) gave evidence that hormones of the adrenal cortex accelerate changes when administered to spontaneously metamorphosing amphibian larvae or to amphibian larvae that have been treated with TH. On the other hand, other early investigations produced evidence indicating that application of corticosteroids to young larvae resulted in inhibition of metamorphic events (Gashe, 1942; Kobayashi, 1958). Another possibility is suggested by the observation of Buscaglia et al. (1981) to the effect that metamorphic arrest by corticosterone in young larvae of *Xenopus* is associated with decreases in the concentrations of T₃ and T₄. Possibly in early developmental stages, corticoids act on the hypothalamus, pituitary or thyroid to reduce thyroidal activity.

More recent studies appear to have established firmly that adrenocortical steroids can synergise with TH in the stimulation of metamorphosis. Observations made on pieces of tail cultured *in vitro* have been particularly enlightening. Isolated tail tissues regress readily when exposed to TH in culture but the shrinkage is preceded by a latent period which can be shortened by the addition of cortical steroids (Kalten-
In a dose-dependent fashion, deoxycorticosterone acetate was shown to accelerate shrinkage of cultured tail segments of Japanese toads, *B. bufo japonicus*, when either T$_3$ or T$_4$ were present, even in threshold concentrations, but not in their absence, indicating the corticoidal action to be one of enhancement (Kikuyama et al., 1983). In addition to these *in vitro* studies, support for the proposition that corticoids have a role in the regulation of metamorphosis comes from the observation that injection of Amphenone B, an inhibitor of corticoid synthesis, retards both induced and spontaneous metamorphosis in toad tadpoles (Kikuyama et al., 1982).

Since it is clear that cortical steroids synergise with TH in the promotion of metamorphosis, one next inquires: what is the mode of action of the steroids in that synergism? Enhancement of binding capacity for TH appears to be a significant answer. Binding capacity for T$_3$ in the tails of Japanese toads (Niki et al., 1981) and nuclear binding of T$_3$ in tail segments of *R. catesbeiana* (Suzuki and Kikuyama, 1983) were increased by both of the principal amphibian adrenocorticoids (Carstensen et al., 1961; Crabbe, 1961), corticosterone (CC) and aldosterone (A); CC by 41% and A by 60%, correlating with the observation that A is also more effective than CC in stimulating resorption of the bullfrog tail (Kikuyama et al., 1982). The increases induced by both CC and A were blocked by cycloheximide, an inhibitor of protein synthesis, and by actinomycin D, an inhibitor of RNA synthesis, indicating that the synergistic interaction required synthesis of new protein and new RNA(s) (Suzuki and Kikuyama, 1983).

One of the paramount features of anuran metamorphosis is an extensive remodeling of the gut that occurs while the herbivorous tadpole is transformed into a carnivorous frog or toad. During prometamorphosis and early climax, insulin-producing cells of the islets of Langerhans multiply and give histochemical signs of hyperactivity (Cheng-Kaung, 1983). Levels of I in serum and in the pancreas rise in confirmation of the histological observations (Hulsebus and Farrar, 1985). It has now been shown that insulin may interact with hydrocortisone to modify the enzymic activities of the new brush border that forms during the late phases of metamorphosis in the obstetrical frog, *Alytes obstetricans* (El Maraghi-Ater et al., 1986), signifying the involvement of yet another synergistic interaction.

The patterns of differentiation and the beginnings of function in the interrenals follow closely the patterns of metamorphic change (Rapola, 1963; Dodd and Dodd, 1976). The first measurable amounts of steroid in the interrenals are detected just before the onset of climax. Cytological evidence of physiological activity is greatest in interrenals of *Xenopus* at mid climax (Rapola, 1963). The concentrations of steroid metabolites in excretions increase at the beginning of climax and continue at a high level with a peak near the end of metamorphosis (Dale, 1962).

Serum levels of the major corticoids have been followed throughout metamorphosis by RIA: CC in *R. catesbeiana* (Jaffe, 1981; Krug et al., 1983), A in *R. catesbeiana* (Krug et al., 1983; Kikuyama et al., 1986) and both CC and A in *Xenopus* (Jolivet Jaudet and Leloup Hatey, 1984). Although there is general agreement that levels of both these hormones peak at metamorphic climax, Krug et al. (1983) found indication of an additional lesser peak in CC during prometamorphosis and Jolivet Jaudet and Leloup Hatey (1984) found one in A during the same period.

These increases in adrenocortical steroids during metamorphosis may be attributable to the well-documented build-up in TH described in the preceding section of this paper. There are several ways in which TH might act to increase levels of corticoids. One line of reasoning is as follows: In the Amphibia, unlike the Mammalia, the adrenocorticotropic hormone (ACTH) stimulates the release of both A and CC from perfused amphibian interrenals (Maser et al., 1982). By an indirect histochemical method, levels of ACTH (or an ACTH-like factor) have been shown to increase in larvae of *R. catesbeiana* from an initial low level to a peak during metamorphic climax (Yu et al., 1985).
accompanying the increases in TH and corticosteroids. Synthesis of anuran corticotropin-releasing hormone (CRH) is localized in the region of the optic chiasma (Jorgensen, 1976; Notenboom et al., 1976). CRH must traverse the ME (Ball, 1981) to reach the corticotropic cells of the pars distalis. Etkin (1963, 1966) observed that while the tadpole approaches climax its ME reaches an advanced state of development (such as would be required for transport of CRF). Those workers produced the same state of differentiation in the ME by injecting thyroidectomized tadpoles with T4. Then, one may conclude, the climactic peak in adrenal steroids could result in part from the fact that TH stimulate the differentiation of the ME, increasing the amount of CRF that reaches the corticotropes of the adenohypophysis, causing a rise in the rate at which ACTH is released to produce the peak of adrenal steroids in the bloodstream.

Another consideration is the finding of Kikuyama et al. (1986), that TH may raise levels of A in the plasma, either by acting synergistically with ACTH or by acting alone. Kikuyama et al. (1986) suggest that in the amphibian, although ACTH promotes the release of A by acting directly on the interrenals, a renin-angiotensin system is present also (Nishimura, 1980) and might be activated by TH to bring about the release of A.

It is also possible that TH may in some way have the capacity to act directly on the synthesis of enzymes by interrenal cells. Hsu et al. (1984) have shown that administration of T4 raises levels of the corticoidogenic enzyme, Δ4-3β-hydroxysteroid dehydrogenase, in hypophysectomized bullfrog tadpoles.

The diagram in Figure 1 is an attempt to summarize schematically the various ways in which the thyroid and the interrenals may interact to bring about metamorphic changes.

**Prolactin**

**Antagonism with TH**

Regulation by interaction between opposing factors is a common occurrence in biological systems. Indication that prolactin (PRL) acts antagonistically to TH in amphibian metamorphosis was first inferred from the results of Etkin and Lehner (1960) who noted that both thyroidectomized tadpoles and tadpoles bearing ectopically positioned grafts of pituitary glands both failed to metamorphose and, at the same time, grew more rapidly than control animals. With great scientific insight, they suggested that prolactin might be a factor in those results. The validity of that suggestion was borne out in a variety of investigations that became possible when purified PRL became readily available for purposes of research (see Clarke and Bern, 1980; Dent, 1985).

**Antagonism at the glandular level**

Studies aimed at discovering whether or not prolactin exerts an effect on the thyroid glands of anuran larvae have produced conflicting results. It was reported that injections of oPRL caused the uptake of radioactive iodine to be lowered in the thyroid glands of prometamorphic frog tadpoles but to have no effect on the thyroid glands of tadpoles at metamorphic climax (Gona, 1968). In larvae of *Xenopus*, PRL reduced the stimulatory effect of TSH on thyroidal epithelium (Regard and Houdry, 1975) and depressed thyroidal uptake of 131I during prometamorphosis and climax (Dodd and Dodd, 1976). Conversely, larvae of the toad, *B. bufo*, responded to oPRL with an increased uptake of radioactive iodine (Campantico et al., 1968).

Apparent contradictions are also seen among the urodèles. The thyroidal uptake of 131I in neotenic specimens of *A. tigrinum* was unaffected either by the administration of the ergot alkaloid, ergocornine, that inhibits the secretion of PRL (Platt, 1976) or by the injection of oPRL (Norris and Platt, 1973). In neotenic *A. mexicanum*, oPRL failed to block TSH-induced release of T4 (Darras and Kühn, 1984). On the other hand, when *A. tigrinum* larvae were injected simultaneously with oPRL and TSH, the stimulatory effect of TSH on circulating levels of T4 was cancelled (Norris, 1978), and in the red eft, the terrestrial, juvenile phase of the red-spotted newt (*Notophthalmus viridescens viridescens*), oPRL...
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lowered the uptake of $^{131}$I (Waterman and Grant, 1961). The inconsistent nature of these findings precludes a firm conclusion, but suggests that under some conditions PRL may have a marginal inhibitory effect on the thyroid gland.

Peripheral interaction

Several investigations have demonstrated conclusively that antagonistic interaction occurs peripherally because it takes place when TH and PRL are administered together to anuran larvae (Derby and Etkin, 1968; Derby, 1975) or to tail segments of urodele larvae maintained in vitro (Platt et al., 1978).

Mechanisms of Interaction

The next four subsections serve to outline different mechanisms by which TH and PRL may interact antagonistically during metamorphosis.

Enzymic action

A variety of hydrolytic enzymes accompany, and apparently accomplish, the regression and remodeling of tissues which take place during metamorphosis (see Dodd and Dodd, 1976). Many of these enzymes are characteristically found in lysosomes, but analysis of regressing tail tissue has indicated that they are present in soluble as well as particulate or membrane-bound fractions (Weber, 1969; Campantico et al., 1972; Greenfield and Derby, 1972). Injection of tadpoles with PRL diminishes the increase in activity of several of the hydrolytic enzymes that are induced by TH (Blatt et al., 1969; Jaffe and Geschwind, 1974; Derby, 1975). This finding supports the
hypothesis that at least some portion of the antimetamorphic action of PRL results from a reduction in the activity of those degradative enzymes.

The introduction of TH into media in which pieces of tail are being cultured results in regression of those explants and increased specific activity of the hydrolytic enzymes within them (Tata, 1966; Hickey, 1971; Greenfield and Derby, 1972). Time courses of response to TH in vitro are similar to and in correlation with the sorts of cytological alterations observed in vivo (Gona, 1969).

Prolactin has been shown to inhibit regression of tail slices in vitro (Yamamoto et al., 1979) and hydrolytic enzymes have been examined in explants of tail containing implants of pituitary glands (Derby, 1975) but exposure of explants simultaneously to TH and purified PRL has been lacking. We (Ray and Dent, 1986a) conducted a study in which tissue resorption and specific activities of hexosaminidase (Hex) and of acid phosphatase (AP) were followed in explants of tail fin from R. catesbeiana cultured in medium containing T₄, PRL, or T₄ plus PRL. We found that PRL inhibited regression in a dose-responsive manner, but did not affect specific activity levels of either Hex or AP. We concluded that inhibition of enzymes is not an essential factor in the inhibitory effect of prolactin on the resorption of the tail fin in R. catesbeiana. A similar conclusion was reached by Platt et al. (1986) with respect to metamorphosing larvae of the tiger salamander, A. tigrinum. They injected T₄ and PRL and then measured activities of AP. They observed that in short-term treatment, PRL blocks regression of the fin but not a rise in levels of AP, suggesting that the effect of PRL on hydrolyases is not a prerequisite for its inhibitory action.

Through osmoregulatory action PRL may induce shrinkage without evoking enzymic action. We (Ray and Dent, 1986a) suggested further that the inhibitory effect of PRL on T₄-induced enzymic activity, that was seen in intact animals but not in cultures of fin, did not result from an incapacity of the fin to respond but rather from the absence of some sort of indirect systemic factor which is present in the intact animal. Such a factor has been reported by Nicoll and his collaborators (Anderson et al., 1982, 1984). Direct effects of PRL are sometimes enhanced or supplemented by the induction of an insulin-like growth factor called synlactin (Anderson et al., 1982) which was first shown to potentiate the mitogenetic effect of PRL on the avian crop sac (Anderson et al., 1984). Evidence is now presented to indicate that a PRL-stimulated hepatic factor, presumably synlactin, mediates the promotion of tail growth in the tadpole (Delidow et al., 1986). Perhaps synlactin or some other sort of mediating factor was lacking in our culture medium.

Osmoregulatory effects

Among vertebrates in general, perhaps the major action of PRL is the regulation of water and electrolyte balance (Bern, 1975; Nicoll, 1981). In a series of studies, Platt and his collaborators have produced evidence that the antimetamorphic effects of PRL stem, at least in part, from its osmoregulatory action. The reduction in gill length and tail height of neotenic tiger salamanders in response to injection with a metamorphosis-inducing dose of T₄ is correlated with loss of water and sodium. Injection of PRL reverses both the regression and the losses (Platt and Christopher, 1977). Retention of water and sodium is also shown to be enhanced in explants of tail fin from metamorphosing larvae cultured in medium with PRL added (Platt et al., 1978). The possibility of an osmoregulatory contribution to the antimetamorphic action of PRL is supported further by the finding that its antimetamorphic effects are consistently inhibited by the neurophyseal peptides, oxytocin (Platt and Licause, 1980), lysine vasopressin and arginine vasotocin (Platt and Hill, 1982) and the corticosteroid, aldosterone (Platt and Hill, 1982), all of which are known to have osmoregulatory actions. In this instance, aldosterone may have acted to enhance the binding of TH (Suzuki and Kikuyama, 1983), rather than as an osmoregulator.

In addition, it should be noted that Kikuyama et al. (1983) found that PRL blocked
the enhancement of shrinkage in tail segments from *R. catesbeiana* caused by deoxy-corticosterone acetate which has some mineralocorticoidal action. Also, as pointed out in a preceding section, White and Nicoll (1979) observed that renal binding of PRL is low during premetamorphosis in the bullfrog but increases during climax, signalling a shift in the participation of PRL in the control of hydromineral levels.

**Cyclic AMP**

In those instances in which the actions of TH (Dratman, 1978) and of PRL (Rilllema, 1980) have been most thoroughly studied, little evidence has been found to implicate cAMP as a mediator of the effects of either TH or PRL. Stuart and Fischer (1978, 1979), however, have reported that in explants of tail from larvae of *R. catesbei ana*, levels of Hex rise in response to exogenous cAMP, mimicking the action of TH. Further, they found that T _4_ raised the levels of cAMP in explants and that inhibition of the breakdown of endogenous cAMP by phosphodiesterase enhanced the elevation of Hex by T _4_. These observations were interpreted to indicate that, at least to some extent, the stimulation of metamorphic change by TH is mediated by cAMP.

Conversely, Yamamoto et al. (1979) found that treatment of tail segments from *B. bufo* with dibutyryl cAMP (DBcAMP) suppressed to the same degree as PRL the shrinkage and the degenerative histological changes induced by T _4_. Also, PRL induced a rise in levels of cAMP and inhibition of phosphodiesterase increased the antimetamorphic action of PRL.

We (Ray and Dent, 1986a) followed up the preceding studies using explants of tail fin from bullfrog tadpoles. When explants were cultured in a solution containing T _4_, shrinkage was reduced in a dose-responsive manner by DBcAMP and inhibition of phosphodiesterase antagonized the shrinking action of T _4_ on explants. The mimicking of the action of PRL was complete in that, as we had found with PRL (Ray and Dent, 1986a), DBcAMP did not affect levels of Hex in the explants. In agreement with Yamamoto et al. (1979), our data support strongly the view that cAMP can inhibit resorption of the tail fin. Since, however, we found no alteration of endogenous levels of cAMP by either PRL or TH, the relation of cAMP to the interaction of TH and PRL is not clear. Yet, it is of interest that an analogous effect of cAMP is seen in another instance of hormonally controlled cell death, namely, the effect of DBcAMP in opposing the action of the Müllerian inhibiting substance that causes the regression of the Müllerian duct in the developing male rat (Ikawa et al., 1984) and probably in the male alligator as well (Harriet Austin, personal communication). Perhaps additional study of the sensitivity of these degenerative processes to cAMP may help elucidate the presently unknown mechanism by which the hormones involved induce cell death in their respective target tissues.

**Receptor binding**

Many of the still puzzling physiological aspects of amphibian metamorphosis might be clarified by a more complete understanding of the hormonal receptors involved. A wide variety of studies in birds and mammals indicate that PRL shows a high degree of specific binding to established and suspected target organs (White and Nicoll, 1979).

Nicoll and his collaborators (White and Nicoll, 1979; White et al., 1981) examined the specific binding of PRL in larvae and metamorphosing individuals of *R. catesbeiana*. They found that binding levels were quite stable in samples from tail and gills, which are representative larval organs, and very low or undetectable in liver, which other studies (Blatt et al., 1969; Jaffe and Geschwind, 1974) indicate to be unresponsive to PRL and which undergoes little metamorphic alteration. Confirming observations have been made by J. E. Platt (personal communication).

I have, in a preceding section, commented on the observed rise in renal binding and its osmoregulatory significance. Another example of antagonistic interplay between TH and PRL became apparent during the examination of renal binding. Exposure to T _4_ greatly increased the bind-
ing of PRL, whereas PRL itself acted to inhibit that response (White et al., 1981). In this instance, TH appears to enhance by antagonistic means an effect of PRL that is metamorphic rather than developmental or somatotrophic in nature.

Findings somewhat contradictory to those of the Nicoll group have been reported by Carr et al. (1981). Discrepancies between the two sets of results may have come about through differences in methodology, but a need for further study of this area is indicated.

Prolactin levels during metamorphosis

The doctrine that metamorphosis is regulated by antagonism between TH and PRL having gained broad acceptance (Bern et al., 1967; Etkin and Gona, 1967; Dodd and Dodd, 1976), it was generally anticipated that blood levels of PRL would decline in late preclimax or early climax while thyroid levels rose. In 1977, however, Clemons and Nicoll, using an homologous RIA, showed that plasma and pituitary levels of PRL in bullfrog tadpoles were low until climax and then, instead of falling, rose significantly to fall only at the very last phase of climax, Taylor and Kollros (TK) stage XXV (Taylor and Kollros, 1946). Those results were later confirmed (Yamamoto and Kikuyama, 1982; Yamamoto et al., 1986). It was also demonstrated that PRL cells were more abundant in pituitaries at late climax than at earlier stages and that synthesis of PRL, as monitored by incorporation of [3H]leucine, elevated gradually and remained high during climax (Yamamoto et al., 1986).

The prolactin surge

The discovery that PRL levels rise steeply during the period of greatest metamorphic change was met with some degree of consternation. It was speculated, however, that the impact of the prolactin surge on metamorphosis might be of little significance, that the climactic events might already have been triggered by TH before the surge takes place. Apparently that is what takes place.

In a series of experiments it was demonstrated by Kawamura et al. (1986) that prior to TK stage XVIII a functional thyroid is required for the continuation of metamorphosis since bullfrog tadpoles thyroidectomized at that stage reverted to a stasis condition. They showed that the thyroid is no longer essential after TK stage XXII because its removal at that point did not interfere with the progress and completion of metamorphosis. One concludes, then, that by TK stage XXII, the climactic events have already been induced by TH.

In another series of experiments (Kawamura et al., 1986), the pituitary glands of some larvae were stalk-sectioned at TK stage XXII and those of others were transplanted to ectopic positions. Although severe of hypothalamic connections at earlier stages prevents climax (Etkin and Lehrer, 1960), both of the operated groups completed climax in unison with control groups. Enhanced levels of PRL were seen in neither operated group, even in stalk-sectioned animals treated with T4. These findings show that the surge has little or no effect on metamorphic events. They indicate also that some sort of hypothalamic factor is essential to its occurrence.

The apparent failure of the surge to interfere with metamorphic changes may signal a decline in the antagonistic action of PRL and may mark the beginning of a postmetamorphic condition. Little attention has been given to postmetamorphic interaction between PRL and TH in anurans, but in urodeles there are marked differences between the interactions of PRL with TH in larvae and those observed in adults (Dent et al., 1973; Dent, 1982, 1985). The discovery of White et al. (1981) that PRL can inhibit its own renal receptors may provide some clue to the meaning of the puzzling surge of prolactin.

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