

The Role of the Pineal Body in Ectotherm Thermoregulation

CHARLES L. RALPH, BRUCE T. FIRTH, AND J. SCOTT TURNER

*Department of Zoology and Entomology, Colorado State University,
Fort Collins, Colorado 80523*

SYNOPSIS. The pineal complex may be a part of the sensory and central neural system controlling thermoregulatory behavior. The pineal and parapineal organs of some ectotherms appear to function as radiation dosimeters, regulating exposure to sunlight. Physiological thermoregulation may be influenced by the pineal complex through cardiovascular adjustments or metabolic rates. Additionally, the pineal organ may exert thermoregulatory effects through the control of brain electrolytes. While the precise mechanisms of action remain to be defined, it is clear that pineal-parapineal organs participate in thermoregulatory adjustments by acting upon the central nervous system.

INTRODUCTION

Instead of inventing novel devices for temperature regulation, animals appear to have simply recruited and modified machinery that originally was used for other purposes (Satinoff, 1978). For example, Cowles (1958) has suggested that the peripheral vasomotor system, for varying blood flow at the body surface, was first exploited by amphibians as a respiratory mechanism. Subsequently it became a heat collector and distributor in reptiles, carrying heat inward and retarding the flow of heat outward, and finally an essential mechanism in endotherms for transfer of internally-generated heat mainly outward.

Pineal organs appear to have been incorporated into several regulatory systems, including reproductive systems and mechanisms that influence the timing of daily and seasonal activities. Apparently they also have been recruited into the thermoregulatory system of vertebrates, at

least in reptiles, birds and mammals (Ralph *et al.*, 1979).

RADIATION SENSITIVITY OF PINEAL AND PARAPINEAL ORGANS

Perhaps the most intriguing evolutionary feature of the pineal complex is the way in which light information is gathered and conveyed to these structures. The intracranial epiphysis or pineal organ appears to have evolved from a directly photoreceptive organ (in fish, amphibians, and some reptiles) to one indirectly receiving photic information from sympathetic pathways, usually involving the lateral eyes (in some reptiles, birds, and mammals) (Kappers, 1971; Oksche, 1971; Moore, 1978). Parapineal organs, which are developmentally associated with intracranial pineal organs, appear to have attained a crucial evolutionary stage (among extant vertebrates) in some anuran amphibians and some lacertilian reptiles (Ralph, 1975), where they are often represented by an extracranial photoreceptive structure known as the frontal organ (in some anurans) or the parietal eye (in some lizards). This phylogenetic scenario is supported by the gross morphological, histological and ultrastructural studies carried out over the past century (Studnička, 1905; Collin, 1971). Detailed electrophysiological analyses of parapineal and pineal structures in ectothermic vertebrates have given further credence to these

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generalizations (Dodt, 1973). Such investigations may allow a broad interpretation of the many diverse and apparently contradictory behavioral and other functions attributed to the pineal complex of ectothermic vertebrates.

Electrophysiological activity of the pineal organ in ectothermic vertebrates so far tested is inhibited by light (Dodt, 1973). However, in extracranial parapineal organs, the electrical properties differ. With respect to the frog frontal organ, achromatic and chromatic responses may be recorded from the frontal nerve (Dodt and Heerd, 1962). The achromatic units are inhibited by light of all wavelengths and exhibit negative-going slow potentials. Chromatic responses also occur in the parietal eye of lizards (Dodt and Scherer, 1968*a,b*; Hamasaki, 1969). In these units, excitatory spike activity, associated with positive-going slow potentials, is elicited by light of long wavelengths (λ max = 515 nm for the frog frontal organ, and 520 nm for the lizard parietal eye). Inhibitory spike activity, associated with negative-going slow potentials, is elicited by light of shorter wavelengths (λ max = 355 nm for the frontal organ and 460 nm for the parietal eye).

The above physiological considerations were historically preempted by studies initiated by Stebbins and his co-workers, relating the parietal eye of lizards to certain aspects of behavior. Removal or shielding of the parietal eye, in laboratory gradients and in field situations, caused increased exposure to bright light, increased basking, enlarged home ranges, and decreased fright reaction (Stebbins and Eakin, 1958; Stebbins, 1963). Increased basking following parietectomy was confirmed in subsequent studies (Packard and Packard, 1972; Stebbins and Cohen, 1973). Light is apparently the primary stimulus regulating such behavior, since parietectomized lizards became exposed to bright light more often than controls in a photic gradient at constant temperature (Stebbins, 1970).

Thus, the parietal eye can be viewed as a radiation dosimeter (Stebbins and Wilhoft, 1966; Eakin, 1973) or, more appropriately,

an illuminometer (Packard and Packard, 1972), regulating exposure of the lizard to sunlight on bright sunny days preceding the breeding season. Steyn (1961, 1966) proposed that the parapineal organs also may warn against dehydration, particularly in frogs, as well as serve as a sensory device in thermoregulation. In an experiment supporting this hypothesis, Adkins (1961) found that toads whose frontal organ was shielded, selected higher light intensities and suffered higher mortality in a desiccating environment.

The peculiar neurophysiological characteristics of the frog frontal organ and pineal organ allow the possibility of a dosimetric function. The frontal organ can integrate changes in chromatic light input for long periods (Donley, 1975). It is also relatively insensitive to adaptation by previous light stimuli (Dodt, 1973). Moreover, when the frontal organ is subjected to steady illumination, as in a natural environment, the firing rate of units in the frontal nerve decreases linearly with the logarithm of increasing luminance, regardless of its wavelength (Hamasaki and Esserman, 1976). Such is not the case in the lizard parietal eye (Dodt, 1973; Hamasaki and Eder, 1977). First, the parietal eye shows significant adaptation to previous light stimuli and, second, it is unable to summate or integrate light responses for long periods. For example, the relationship between the logarithm of the luminance of the stimulus and the firing rate is linear only for up to 0.1 sec (inhibitory component) and 0.4 sec (excitatory component) as compared to about 2 min in the frontal organ.

The intracranial pineal organ of lizards may possess characteristics better suited to a dosimetric function. Although not shown for lizards, the achromatic units of photoreceptive pineal organs in many other groups exhibit a linear relationship with the logarithm of the luminance which is independent of light adaptation (Dodt, 1973). The lizard pineal organ is most responsive to red light (600 nm), and requires a relatively high light intensity to alter activity. In the frog, for example, a light intensity of only 10^{-6} to 10^{-3} lm/m² is

required to inhibit spike activity in the pineal organ (Dodt and Morita, 1964), compared to about 5 lm/m² for the lizard pineal (Hamasaki and Dodt, 1969). This has led to the conclusion that the lizard pineal organ could only respond to changes in direct light stimuli during the day and not at night (Hamasaki and Dodt, 1969).

If the lizard parietal eye cannot be considered a dosimeter of solar radiation, the functional effects induced by its impairment may be explained in other ways, such as disruption of locomotor activity responses and daily and seasonal rhythmicity. Many non-mammalian vertebrates respond to light perceived through extraretinal photoreceptors (Adler, 1976; Menaker and Underwood, 1976; Underwood and Menaker, 1976). Among amphibians, extraretinal receptors may entrain circadian activity rhythms to the prevailing light cycle (Adler, 1971, 1976; Justis and Taylor, 1976; Demian and Taylor, 1977). In some cases, the pineal complex has been implicated in these responses. In blinded *Rana clamitans*, the entrainment to light cycles is abolished by removal of the frontal organ (Adler, 1971). Removal of the pineal organ of newts (which lack a frontal organ) eliminated the difference in activity patterns between animals exposed to a light cycle and those exposed to constant light, presumably by preventing entrainment (Demian and Taylor, 1976).

In contrast, neither the parietal eye nor the pineal organ of blinded lizards is necessary for the entrainment of activity rhythms (Underwood and Menaker, 1970). However, the parietal eye may exert a more subtle influence on circadian activity. For example, Glaser (1958) found increased activity upon shielding the parietal eye of desert night lizards, *Xantusia vigilis*. Also, Palenschat (1964) and Firth (1974) found differences in the activity pattern between normal and parietalectomized lizards subjected to light of differing spectral characteristics.

The pineal organ of lizards appears to be more overtly involved in circadian organization than the parietal eye. Under

constant light, parietalectomy and pinealectomy together caused the activity rhythm to be either split into two independent components, or radically altered in some other way (Underwood, 1977). This effect has been viewed as a demonstration that the pineal organ of lizards is either a master oscillator, or a single component in a multi-oscillatory circadian system. In the above experiments, parietal eye participation in such an effect was discounted, since its removal alone did not alter circadian activity and also because it was assumed that pinealectomy abolished the innervation, and hence the function, of the parietal eye. Such may not be the case, however, as indicated by our experiments on temperature selection (see next section).

A phenomenon not unrelated to circadian organization is that of sun-compass orientation, since it must necessarily involve perception of the sun's position relative to the time of day (Hoffman, 1972). A number of studies, particularly those involving frogs and salamanders, have shown that extra-retinally perceived cues may be employed in this type of orientation (Landreth and Ferguson, 1967; Taylor and Ferguson, 1970; Taylor, 1972), and, further, that the pineal complex is a possible site for the perception of such cues (Justis and Taylor, 1976; Taylor and Adler, 1978). In addition, it has been suggested that linearly polarized light cues may be important in this mechanism, since such patterns bear a fixed relationship to the sun's position (Adler and Taylor, 1973; Hamasaki and Eder, 1977). It may be informative, in this context, to cite the work of Van der Glas (1975, 1976) who proposed that bees perceive the polarization pattern of the sky for orientation purposes, by integrating the spectral input to two or more color receptors within the ommatidia. It is, therefore, conceivable that the color-opponent system of the frontal organ and parietal eye could operate in a similar way. Indeed, the suggestion has been made that the chromatic system of parapineals may be used to detect the angle of the sun, since the proportion of ultraviolet and visible light vary with the sun's angle (Donley, 1975).

BEHAVIORAL THERMOREGULATION

Ectotherms have evolved complex behavioral mechanisms to attain and regulate body temperature. In lizards, for example, this may involve various postural changes and orientational adjustments, burrowing, variations in diel activity, and, most importantly, shuttling behavior (Schmidt-Nielsen and Dawson, 1964; Heath, 1970; Heatwole, 1970, 1976; Templeton, 1970).

In many ectotherms, the upper range of optimal temperatures during activity may very nearly approach their lethal limits (Hamilton, 1974) and so must be carefully regulated. Central neural and humoral mechanisms in all ectotherms very likely involve the hypothalamus and related brain structures (as is true in avian and mammalian thermoregulatory control), evidence for which has been provided in fish (Hammel *et al.*, 1969; Greer and Gardner, 1970; Crawshaw and Hammel, 1971, 1973) and lizards (Cabanac *et al.*, 1967; Hammel *et al.*, 1967, 1973; Myhre and Hammel, 1969; Kluger *et al.*, 1973; Berk and Heath, 1975).

The pineal complex may participate in the central mechanisms controlling thermoregulatory behavior. Since much of the relevant data is derived from lizards, we will confine most of our generalizations to that group.

Several studies (cited in the preceding section) demonstrate that the parietal eye inhibits exposure to bright sunlight and may also alter other responses related to activity (Glaser, 1958; Palenschat, 1964; Firth, 1974). Such behavioral changes are compatible with altered thermoregulatory ability, insofar as increased exposure and activity would increase the amount of time spent at optimal thermal levels (Eakin, 1973). Indeed, Stebbins and Eakin (1958) noted that in *Sceloporus occidentalis* which had undergone parietal eye shielding, body temperatures above 37.5°C were recorded more frequently than in controls.

Recent investigations, utilizing equipment for the continuous monitoring of thermal information, have directly addressed the question of parietal eye involvement in thermoregulation. Roth and

Ralph (1976) found that parietectomized *Anolis carolinensis*, exposed to a moving photothermal source in the laboratory, selected higher temperatures than control lizards. This effect was evidently unrelated to a light dosimetric function, since a supplementary study showed that parietectomized *A. carolinensis* selected higher temperatures than sham-operated controls, independent of light stimuli (Roth and Ralph, 1977). Similarly, Hutchison and Kosh (1974) demonstrated that parietectomized anoles, in a thigmothermal gradient with an imposed photoperiod, selected higher temperatures than controls, both day and night, except between 0800 hr and 1200 hr. Furthermore, the diel cycle of temperature selection in the experimental group was 3 hr out of phase with the controls (maximum at 1600 hr compared to 1300 hr). Engbretson and Hutchison (1976), utilizing an experimental apparatus similar to that employed by Hutchison and Kosh, found that parietal nerve transection in *Sceloporus magister* also resulted in selection of higher temperatures. However, in contrast to the previous study, there was no difference between experimental and control groups in the timing of maximum daily temperatures. Also, the largest difference in body temperature between control and experimental lizards occurred in the photophase in *S. magister*, and during the scotophase in *A. carolinensis*.

It is apparent from the above investigations that the parietal eye has a direct effect on thermal selection, complementary to any function as a light dosimeter. If the theory of light dosimetry for the parietal eye relates to thermal selection in lizards, then increasing light intensity elicits greater parietal inhibition of basking. Thus, parietectomy would facilitate basking behavior. This fails to resolve why parietectomy should also induce hyperthermia in the absence of bright light, where the parietal eye would not be expected to operate as a dosimeter.

Although pinealectomy might be expected to elicit similar behavioral thermal responses to those of parietectomy, two lizard studies suggest that this is not so.

Stebbins (1960), upon observing the effects of pinealectomy in a field population of *S. occidentalis*, reported a significantly lower body temperature than controls. In addition, none of the differences with respect to activity and exposure to sunlight recorded for parietalectomized lizards were observed following pinealectomy. Experiments on the effects of pinealectomy on thermal selection in *Crotaphytus collaris* in outdoor runways (Firth, Mauldin and Ralph, in preparation), are in agreement with those of Stebbins, and indicate an interesting and unexpected relationship between the role of the pineal organ and the parietal eye in behavioral thermoregulation in this species (Fig. 1).

We conducted these experiments during the late summer and early fall; one to test

the effect of parietalectomy on temperature selection; the other testing the effect of either pinealectomy alone, or together with parietalectomy. It was deemed necessary to run the experiments separately because of the limitations of space and temperature-measuring equipment. Following parietalectomy no significant difference was observed between the experimental and sham-operated control lizards. Following pinealectomy, however, lizards consistently selected lower temperatures than controls. In addition, *C. collaris* that had undergone both parietalectomy and pinealectomy selected even lower temperatures than pinealectomized lizards (Fig. 1).

We are unable at this time to account for the lack of a hyperthermic response to pinealectomy in *C. collaris*. We can only suggest that the discrepancy between this and other species is due to seasonal effects, exposure to sunlight (rather than lamps as in other studies), or species differences. We do not know why parietalectomy should act only in concert with pinealectomy, especially when pinealectomy alone probably disrupts the innervation of the parietal eye (Stebbins, 1960; Underwood, 1977). However, the innervation may remain intact, or the parietal eye may be secretory. The latter possibility is not borne out by morphological and ultrastructural data (Eakin, 1973). On the other hand, large amounts of hydroxyindole-O-methyl transferase (HIOMT) (an enzyme necessary for melatonin synthesis) have been located in the parietal eye of iguanid lizards (Quay, 1965a).

Nevertheless, these data suggest that the pineal complex modulates nervous centers concerned with behavioral thermoregulation. There may be an interaction between the pineal and the parietal eye in this response, or both may impinge upon such centers independently of one another. There is reason to suggest a parietal-pineal interaction, since in *C. collaris* the neurotransmitter-related, afferent impulse activity in the parietal nerve may be modified by light conditions (Engbretson and Lent, 1976). Also, parietalectomy has been found to increase pineal HIOMT activity in lizards (*S. occidentalis*) subjected to

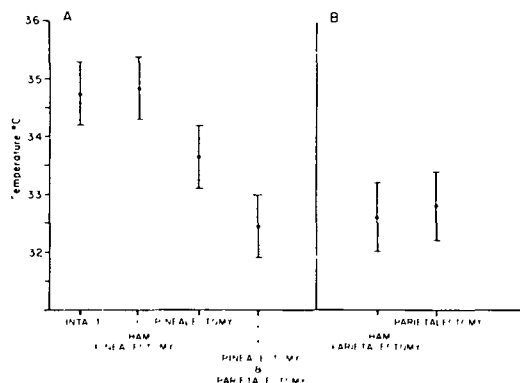


FIG. 1. Thermal selection in outdoor runways by *Crotaphytus collaris* subjected to various surgical procedures. Means represent, for each treatment group, the average accumulation of temperatures selected at the 60th percentile over several days (i.e., one temperature was obtained for each lizard, each day, by ranking the 50 daily temperatures recorded from each animal from 7 A.M. to 7 P.M., and selecting the 20th highest). Vertical lines represent the honest significant difference (Tukey's multiple-comparison test). Non-overlap indicates a difference significant at the 5% level. A. Effect of pinealectomy alone, and parietalectomy and pinealectomy together (5-6 animals per group, 9 days of data). B. Effect of parietalectomy (4-5 animals per group, 4 days of data). Note that mean values in this experiment are lower than those of comparable treatments in A, due to lower environmental temperatures on the days that experiment B was conducted. Analysis of variance showed significant day-to-day variation in thermal selection because of day-to-day fluctuations in maximum environmental temperatures.

high light intensity (Bethea and Walker, 1978). Furthermore, Firth and Kennaway (in preparation) have demonstrated that parietectomy abolishes the diel rhythm of plasma melatonin in the lizard *Trachydosaurus rugosus* exposed to both a light and temperature cycle. We may no longer assume, however, that all circulating melatonin is secreted by the pineal, since other sources have been identified (Gern *et al.*, 1978a).

Through which neural centers might the pineal complex exert its thermoregulatory influence? As was mentioned previously, certain areas in and around the hypothalamus of lizards participate in behavioral thermoregulation. Cabanac *et al.* (1967) recorded extracellular action potentials from warm-sensitive and cold-sensitive neurons in the hypothalamus of the lizard, *Tiliqua scincoides*. Hammel *et al.* (1967) observed in the same species that when the lizard was in a hot environment, heating of the preoptic region resulted in exit behavior prior to the time that body temperatures normally reached optimal levels. Cooling of the brain caused later retreat from the hot area. Myhre and Hammel (1969) performed similar experiments which showed that peripheral as well as brain temperatures may be important in the behavioral thermoregulatory responses of lizards. The medial and periventricular preoptic areas of *Dipsosaurus dorsalis* possess neurons controlling the high and low temperature set-point mechanisms responsible for shuttling behavior (Berk and Heath, 1975). This area is homologous to the major thermoregulatory control center of birds and mammals.

Another aspect of reptilian thermoregulatory behavior possibly relating to the pineal complex may involve thermoregulatory rhythms and voluntary hypothermia (Regal, 1967). Such behavior may be affected by light intensity (Spellerberg, 1974) and there are also indications, that under constant light conditions, such rhythms may persist (Regal, 1974). It has been suggested (Regal, 1967) that this behavior is the evolutionary prelude to the diurnally fluctuating body temperature

exhibited by many birds and mammals (Halberg *et al.*, 1954; Hudson and Kimzey, 1966). In at least one bird species, the house sparrow, such a rhythm is abolished by removal of the pineal gland when the birds are exposed to constant darkness (Binkley *et al.*, 1971), an effect similar to that demonstrated for circadian locomotor activity (Gaston and Menaker, 1968). In the case of mammals (rat), the temperature rhythm is controlled partly by the suprachiasmatic nucleus (Stephan and Nunez, 1977), to which there is a retino-hypothalamic tract for the mediation of photic information (Moore, 1978). In this context, it is interesting that lesions in the anterior hypothalamic nucleus and the suprachiasmatic nucleus of the lizard, *D. dorsalis*, disrupt mechanisms involved in seeking cooler temperatures, especially the arousal mechanism from voluntary hypothermia (Berk and Heath, 1975). An increase in the period of voluntary hypothermia has also been reported in *D. dorsalis* following lesions in the posterior hypothalamus, particularly of the mammillary bodies (Kluger *et al.*, 1973). Thus, our studies on the effects of pinealectomy could be interpreted as a prolongation of hypothermia, although it might also be interpreted as a lowering of the thermal preferendum, since there appeared to be no significant difference in emergence times between the various post-surgical groups.

There is little anatomical evidence in lizards to support the notion that there is a direct nervous connection between the pineal complex and the hypothalamus. The parietal nerve of lizards has been traced to the left habenular nucleus (Eakin, 1973). The pineal tract in both frogs (Paul, 1971) and lizards (Kappers, 1967) reaches the region of the periventricular gray, but the sites of termination of the fibers have not been determined. However, in the trout, *Salmo gairdneri*, Hafeez and Zerihun (1974) found that pinealofugal fibers may project into the preoptic region.

Histological and histochemical studies have demonstrated a relationship between the pineal complex and the hypothalamus.

Aron *et al.* (1960) found pinealectomy in the turtle *Emys leprosa* resulted in an increased neurosecretory activity of the paraventricular nucleus. Similarly, Vullings (1973) reported that removal of the frontal organ of frogs, either alone or together with the pineal organ, enhanced incorporation of ^{35}S -cysteine in the preoptic nucleus. It is also notable that although removal of the frontal organ alone did not affect uptake of ^{35}S -cysteine in the posterior lobe of the pituitary, removal of the entire pineal complex enhanced it, indicating that both pineal components may modulate activity in different brain centers.

The most widely studied substance associated with the pineal organ is melatonin, the levels of which vary rhythmically in response to environmental photoperiod in the pineal and/or blood of fish (Fenwick, 1970; Gern *et al.*, 1978b), amphibians (Gern, Owens and Ralph, unpublished), lizards (Firth *et al.*, 1979), birds and mammals (Ralph, 1976). Melatonin has been shown to alter thermal characteristics in birds (Binkley, 1974; John *et al.*, 1978) and mammals (Arutyunyan *et al.*, 1964; Fioretti and Martini, 1968; Fioretti *et al.*, 1974; Palmer and Riedesel, 1976; Lynch and Epstein, 1976; Lynch *et al.*, 1978). The exact site of action of melatonin is unknown, although it has been hypothesized that it acts on the brain (Reiter, 1973; Ralph, 1976). Indeed, several studies have shown accumulation of melatonin in the hypothalamus (*e.g.*, Cardinali *et al.*, 1973, 1978; Mess and Trentini, 1974; Ralph, 1976), cerebrospinal fluid and choroid plexus (Mess and Trentini, 1974; Kovacs *et al.*, 1975). There also may be an interaction between the suprachiasmatic nucleus and the pineal enzyme, serotonin N-acetyltransferase (NAT), which is involved in melatonin synthesis. Suprachiasmatic lesions in the rat either abolished the endogenous rhythm of pineal NAT in constant dark (Moore and Klein, 1974) or reversed the rhythm in a normal light-dark cycle (Raisman and Brown-Grant, 1977).

It is obvious that close attention must be paid to light in studies relating the pineal complex to thermoregulation. As we have

argued, there appears to be an involvement of the pineal complex in activity cycles, which are cued to a great extent by photoperiod. Activity cycles are themselves important in regulating thermal input, particularly in terrestrial ectotherms (Bartholomew, 1959). For example, some desert reptiles have adapted their activity cycles to conform to their thermal and ecological requirements by retreating to their burrows during the hottest part of the day. The possible sensitivity of the pineal complex to the *e*-vector of polarized light (Hamasaki and Eder, 1977) could aid in orienting a heliothermic lizard to gain maximum advantage from the sun's rays during heating and cooling.

Such a relationship between light, thermoregulation and the pineal may not be confined to ectotherms. Circadian light cues are necessary for effective thermoregulation in monkeys (Fuller *et al.*, 1978). Pinealectomized chickens subjected to heat stress show thermoregulatory dysfunction in the night but not during the day (Cogburn and Harrison, 1977). In rats, Spencer *et al.* (1976) noted that a relationship between photoperiod and mean daily body temperature was abolished following pinealectomy.

COLOR CHANGE

Many ectothermic vertebrates can rapidly change their skin color or pattern. These physiological responses result from selective changes in the disposition of chromatophore pigments (Bagnara and Hadley, 1973).

Color change, in many situations, is an adaptation that confers protective coloration. Among lizards, color change can function as an adaptation for thermoregulation as well as for concealment (Norris, 1967). Thus, the two functions are not necessarily mutually exclusive.

Color change is not always relevant to thermoregulation, however. It is impossible for the vast majority of fishes and frogs (Hogben and Kirk, 1944; Tracy, 1978) to significantly alter their body temperatures through color change, due to excessive conductive, convective or evaporative heat

loss. (But for an alternative view, see Brattstrom, 1962, 1970).

Desert lizards illustrate most clearly the relationship between coloration and body temperature regulation (Norris, 1965). Through a combination of behavioral and color change mechanisms, lizards effect a rather high degree of temperature regulation. When cool, they typically have a dark skin, which absorbs incident light and heat (Atsatt, 1939; Norris, 1967). Later in the day, as the lizards and the environment heat up, coloration, body shape and orientation may be altered to minimize additional heat loading (Parker, 1906, 1938). As temperature falls toward evening, the behavioral and chromatic mechanisms again combine to collect heat. Thus, many species of lizards minimize heat uptake in the middle of the day and maximize uptake toward the ends of the day. Cowles and Bogert (1944), from their study of desert reptiles, concluded that "for diurnal lizards the effect of color change operates to provide an extension of time at marginal thermal levels."

Melanophore-stimulating hormone (MSH), which is characteristic of the pars intermedia of the pituitary gland, is the primary hormone controlling color change (Bagnara and Hadley, 1973). However, there are many variations in the manner in which chromatophores are regulated, including hormonal, neural, and mixed hormonal-neural.

Melatonin is a potent melanosome-aggregating agent. It is especially effective in causing dermal melanophores of anuran tadpoles to concentrate their pigment, resulting in the so-called "body-blanching response." *Xenopus* larvae, when placed in darkness, exhibit body blanching. When "pinealectomized" by cautery of the diencephalic roof, larval *Xenopus* do not blanch in the dark (Bagnara, 1960). This and other observations (Bagnara, 1964) indicate that melatonin may play a role in the chromatic changes of larval amphibians. However, no such role has been demonstrated for adult amphibians (Bagnara and Hadley, 1973). Additionally, there is little convincing evidence that melatonin is involved in the normal control of chro-

matic responses of teleosts (Bagnara and Hadley, 1973).

Melatonin causes lightening of *Anolis* skin *in vitro*, but there is no unequivocal evidence that the pineal complex *per se* is involved in the regulation of color change in any reptile (Bagnara and Hadley, 1973).

Melatonin apparently is not the only chromatophorotropic present in pineal bodies. Rudman *et al.* (1972) have reported the presence of at least two different lipolytic-melanotropic (melanophore-darkening) peptides in ovine and bovine pineals.

If the pineal complex exerts an effect on color change in vertebrates, it seems mostly likely that it does so by influencing the release of pituitary MSH. Supporting this interpretation is the report by Oshima and Gorbman (1969) describing a direct effect of the pineal complex of the frog on neural activity in the pars intermedia (but Dawson and Ralph, 1971, were unable to confirm their result). Disconcertingly, most of the evidence for a pineal influence on pituitary MSH comes from studies with mammals, in which there is no known direct effect on pigmentation. Nonetheless, a brief account of the relevant literature may be of heuristic value.

Pinealectomy increased MSH content of the rat pituitary, according to Kastin *et al.* (1967a). Constant illumination, which presumably suppresses melatonin formation, also increased the MSH content (Kastin *et al.*, 1967b). Furthermore, hypophysectomized rats had higher plasma levels of melanocyte-lightening activity (= melatonin?), as determined by a frog bioassay (Kastin *et al.*, 1972). However, Tilders and Smelik (1975) found that sympathetic denervation of the pineal gland of rats, as well as pinealectomy, did not block the rhythm in pituitary MSH, and had no effect on pituitary MSH content. Furthermore, melatonin administration did not affect MSH levels. Pavel *et al.* (1975), on the other hand, reported that pinealectomy of mice caused a three-to five-fold increase in pituitary MSH, as did constant light. The injection of arginine vasotocin (AVT) into the third ventricle abolished the stimulatory effect of both pinealectomy and con-

tinuous light on MSH content. They believe that melatonin depresses pituitary MSH in mice indirectly by causing the release of AVT which, in turn, alters pituitary MSH levels. AVT, which has been isolated from pineal glands of some mammals (Benson, 1977), is said to be about 108 times more effective than melatonin in depressing pituitary MSH.

Melatonin implanted into male weasels caused development of white coats, whereas unimplanted animals had brown coats (Rust and Meyer, 1969). Because this effect did not occur in animals where the pituitary was grafted under the kidney capsule, it was concluded that melatonin acts on the hypothalamus to prevent MSH release. Other investigations have failed to show an effect of melatonin on pigmentation in mammals other than the weasel (Snell, 1965).

By analogy with mammals, there is the possibility that pineal organs of certain ectotherms, through release of melatonin or another pineal substance, may modulate the secretion of MSH and thereby participate in color change. Thus, in an indirect manner, the pineal complex, including the parietal component which is ideally placed for assessing incident radiation, may play a thermoregulatory role in some reptiles. However, Parker (1938) noted that *Phrynosoma*, which became dark in color under strong illumination, continued to do so whether the parietal eye was covered or not. A similar lack of parietal eye involvement in color change has been demonstrated in *Agama colonorum* (Stigler, 1950). Thus, we are left with great uncertainty about the role of the pineal complex in color change, if any, and, thus, in the regulation of body temperature.

PHYSIOLOGICAL THERMOREGULATION

The pineal complex of lizards has been convincingly shown to be involved in behavioral thermoregulation, as discussed previously. However, very little is known of the role, if any, that the pineal complex plays in the control of the more subtle, yet extremely important physiologic elements

of ectothermic thermal biology. If the pineal complex influences behavioral thermoregulation through hypothalamic thermoregulatory centers, it may be possible that a similar influence applies to physiological thermoregulation. Physiological systems that are implicated in thermoregulation, such as the cardiovascular system (Johansen and Martin, 1965) in reptiles (White, 1976) and frogs (Lillywhite, 1974) and panting thresholds in lizards (Templeton, 1970, 1971; Crawford and Barber, 1974), are under central nervous influence. The observation that an otherwise immobile male *S. occidentalis* can undergo a 2-3°C increase in body temperature at the sight of another male lizard (Engbretson and Livezey, 1972) implies that the brains of these animals are capable of integrating environmental information into a tangible, physiologically-mediated thermal response.

Panting threshold of agamid lizards is one of the few physiological measures of thermoregulation that has been conclusively shown to be affected by manipulations of the pineal complex (Firth and Heatwole, 1976). Parietalectomy of *Amphibolurus muricatus* results in a seasonally-dependent depression of panting threshold when exposed to radiant heat. Exposure to non-radiant heat has the opposite effect. Intraperitoneal injection of melatonin lowers the panting threshold (like parietectomy), while injection of serotonin elevates the panting threshold. The diel variation normally seen in the panting threshold (Chong *et al.*, 1973) is abolished by parietectomy, eye shielding and injections of melatonin, depressing the normally high daytime threshold values. The authors postulate the existence of a light-mediated control system, whereby light information, conveyed via the lateral and parietal eyes, alters the secretion or metabolism of melatonin, which acts on the central nervous system to "set" the panting threshold.

There is some support for this model. Firth and Kennaway (unpublished) have noted an abolition of the diurnal rhythm of plasma melatonin concentration in parietectomized *Trachydosaurus rugosus*,

when the photoperiod was accompanied by a temperature cycle. Furthermore, constant light or constant darkness abolished this rhythm in normal animals (Firth *et al.*, 1979). In a series of experiments carried out on field populations of *S. occidentalis*, Quay *et al.* (1970, 1971) found that pineal HIOMT activities did not vary significantly with time of day (no nighttime samples were taken), but that animals killed and sampled on the coldest day of the experiment had the lowest levels of pineal HIOMT. Parietalectomized animals, interestingly, had the lowest pineal HIOMT levels of any of the groups on the coldest day, suggesting a temperature-parietal eye interaction on pineal indoleamine metabolism. These results should be interpreted with caution, since HIOMT activity may not strictly parallel melatonin levels (Ralph, 1976). Quay *et al.* (1970, 1971) also found that, while cerebral and brainstem contents of serotonin and monoamine oxidase are not affected by parietectomy, they are by alterations in photic or temperature conditions. Thus, temperature has an effect on both pineal and brain indoleamine metabolism. This effect is modulated by photic input, from the parietal eye in the case of the pineal indoleamines, and most likely from the lateral eyes in the case of the brain indoleamines. Whether these interactions would have a direct effect on the determination of central thermoregulatory set-points in reptiles remains to be seen. However, studies on the thermoregulatory actions of serotonin and various indoles in the brains of mammals (Feldberg and Myers, 1963; De Roij *et al.*, 1978) and birds (Hissa and Rautenberg, 1975) suggest that it would.

Oxygen consumption of lizards may also be affected by manipulations of the pineal complex. Daily variations in oxygen consumption of *Sceloporus cyanogenys* are influenced by photoperiod and thermal acclimation (Songdahl and Hutchison, 1972). Removal of the parietal eye alone has no effect on the maximal levels of oxygen consumption, which occur at about the onset of scotophase. Lateral eye removal alone, however, will elevate the maximal levels. Yet removal of both the lateral and

parietal eyes returns oxygen consumption back to the control levels, suggesting, as in the case of the panting thresholds, that the parietal and lateral eyes interact in some way in determining rates of metabolism. No change in oxygen consumption occurred with parietectomy alone in *S. occidentalis* (Francis and Brooks, 1970). However, possible parietal eye-lateral eye interactions were not examined in this case.

The mechanism for the above response may involve alterations of thyroid function. Eakin *et al.* (1959) and Stebbins and Cohen (1973) reported that parietectomy increased thyroid follicular cell height and thyroid function in free-living *S. occidentalis*. Parietalectomy has been shown to interact with temperature and photoperiod in altering levels of thyroxine in *Anolis carolinensis* (Gern, unpublished). Furthermore, thyrotropin-releasing hormone has been localized in the pineal of frogs (Jackson *et al.*, 1977).

Parietalectomy was found to lower the critical thermal maximum of *A. carolinensis*, which is also influenced by photoperiod and acclimation temperature (Kosh and Hutchison, 1972). However, the physiological interpretation that can be derived from this observation is somewhat uncertain.

Since cardiovascular adjustments in patterns of blood flow can play a significant role in determining the thermal resistance of ectotherms, could the pineal complex influence cardiovascular physiology? Early reports indicate that perfusion of the hearts of mammals and frogs with pineal extracts results in tachycardia and elevation of both cardiac output and strength of contraction (Kitay and Altschule, 1954). Administration of pineal extracts to various mammalian species most often causes a fall of blood pressure. However, some studies show either a rise or no change in blood pressure in response to pineal extracts. This inconsistency may be explained by differing potencies of the extracts or the methods of preparation (Kitay and Altschule, 1954; Bergmann, 1955). Pinealectomized animals sometimes respond in anomalous ways to hypertensive agents, such as noradrenaline (Kitay and Altschule,

1954). Recently, postpinealectomy hypertension has been reported by a number of authors in mammals (Zanoboni and Zanoboni-Mucciaccia, 1967; Karpunen *et al.*, 1969, 1973; Hisada, 1974; Holmes and Sugden, 1975) and the daily rhythm of blood pressure in rats is abolished by pinealectomy (Hisada *et al.*, 1976). In one case, post-pinealectomy hypertension was reversed by the inclusion of melatonin in the drinking water (Holmes and Sugden, 1975). However, the efficacy of melatonin administration by this route is questionable, since melatonin is extremely susceptible to oxidation. In fact, many authors (Supniewski *et al.*, 1961; Arutyunyan *et al.*, 1964; Barchas *et al.*, 1967) have reported no effect from melatonin injections on blood pressure in rats.

The role of melatonin in these cardiovascular responses is, thus, somewhat uncertain. Melatonin, when included in the culture medium, has been reported to retard electrical transmission in the atria of isolated ground squirrel hearts (Palmer and Riedesel, 1976), and this may contribute to a decrease in cardiac output in the intact animal, with a possible fall in blood pressure. However, we must appreciate that melatonin is not the only substance of importance produced by the pineal. The mammalian pineal produces several different peptidic components, including arginine vasotocin (AVT) and a "renin-like activity" (based on the ability of a pineal fraction to produce angiotensin) (Benson, 1977). The presence of these vasoactive components points to a role for the pineal in control of blood pressure and, hence, in patterns of blood distribution. The fact that several vasoactive peptides have been shown to induce profound alterations of body temperature in rats (Brown *et al.*, 1977), and that patterns of blood distribution are important in resistance to thermal change in reptiles (White, 1976) are compelling reasons for considering that the pineal complex has a role in these processes.

Francis and Brooks (1970) determined the role of the parietal eye on heart and ventilatory rate at several static temperatures in *S. occidentalis*. These authors found

that parietectomy did not significantly alter either of these parameters. Recent work in our laboratory (Turner, Firth and Ralph, in preparation), subjecting *Crotaphytus collaris* to heating and cooling, confirmed Francis and Brooks' result with parietectomy. However, pinealectomy resulted in an elevation of heart rate at higher head temperatures, but not at higher body temperatures (Fig. 2). At the same time, pinealectomized lizards showed no significant difference in rate of heating and cooling. This lack of difference could be partially explained by covariance in body weight or snout-vent length, and it is our opinion that certain features of our experimental design and a high within-group variance were responsible for the lack of significance of the result. We are uncertain as to the interpretation that should be attached to this result, but we feel that the most compelling explanation would be some effect of pinealectomy on vasomotor tone. If pinealectomy prevents or interferes with the control of cutaneous vasomotor tone that usually occurs during heating and cooling of lizards and other reptiles (White, 1976), this may explain the higher heart rate in the pinealectomized lizards. However, a definite answer will have to await more detailed experiments on the specific cardiovascular events in this response.

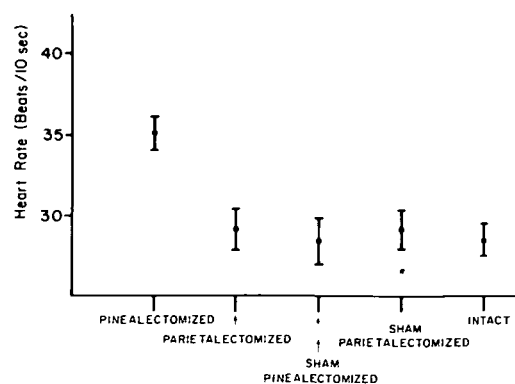


FIG. 2. Heart rate during heating of *Crotaphytus collaris* when head temperature is 38°C. Data are shown as mean \pm one standard error mean. $F_{ANOVA} = 5.33$; $F_{(4,45)} = 2.59$. Heart rates showed the same pattern at the higher head temperatures during cooling as well.

WATER AND IONS IN RELATION TO THERMOREGULATION

In its broadest sense, temperature regulation is a phenomenon of brain function. In this view anything that affects brain function could be expected to have an effect on temperature regulation. Although this viewpoint could seem to generalize beyond the point of utility, it might also offer a fresh perspective.

The regulation of the ionic milieu of the nervous tissue of the brain plays a central role in the proper functioning of neural processes. Although the regulation of brain fluid electrolytes is very rigid (Davson, 1967), it is not constant. The brain exhibits regional, daily and seasonal variations in electrolytes (Davis, 1974), which may be adaptive in some way, perhaps in regulating resting potentials, and, hence, excitability of individual neurons and assemblages of neurons (Woodbury, 1954; Reiter and Morgan, 1972). The possibility that the pineal exerts its thermoregulatory influence through the control of brain electrolytes is a provocative one to us, since it may represent a fundamental mechanism of action for the pineal complex. This is particularly attractive in view of the bewildering variety of effects that have been attributed to the pineal complex, effects which, if taken at face value, are both pervasive and extremely subtle.

In spite of the rather striking morphological diversity of the pineal complex (Hamasaki and Eder, 1977), there are common aspects of its morphology that are suggestive of a role in maintenance of brain hydromineral balance. The most compelling feature along these lines is the association of the pineal body with the paraphysis, a choroid plexus-like tissue that is continuous with the third ventricle choroid plexus. Such an association is evident in amphibians (Kappers, 1965; van de Kamer, 1965), lizards (Lierse, 1965; Gundy and Wurst, 1976), turtles (Owens and Ralph, 1978), birds (Ralph and Lane, 1969) and mammals (Reiter *et al.*, 1974; Gregorek *et al.*, 1977).

The function of the paraphysis of ectothermic vertebrates is believed to be simi-

lar to that of the choroid plexus, *i.e.*, regulation of the cerebrospinal fluid (Shuangshoti and Netsky, 1966). However, Kappers (1956) considers the paraphysis to be a glandular structure in amphibians. Yet, there is evidence to suggest a role for the amphibian paraphysis in ionic or osmotic regulation. The size of the nuclei of paraphysial cells of the tiger salamander neotene (*Ambystoma tigrinum*) decreases with increasing salinity, while the cells of the pars distalis do not exhibit such a response (Turner, unpublished).

A functional association between the pineal and paraphysis is equivocal, however. Although melatonin binds very strongly to choroid plexus (Mess and Trentini, 1974; Kovacs *et al.*, 1975) and the choroid plexus of the third ventricle transports intact ³H-melatonin into the cerebrospinal fluid from the blood (Mess and Trentini, 1974; Kovacs *et al.*, 1975), the typical direction of blood flow is from the paraphysis to the pineal, and not vice-versa, as one would expect for a functional relationship (Quay, 1973; Gregorek *et al.*, 1977).

Nevertheless, a functional role for the pineal complex in the control of brain homeostasis cannot be excluded. The pineals of many ectothermic vertebrates possess a central lumen, which communicates directly with the third ventricle (Hamasaki and Eder, 1977). In the rat, Quay (1974) has noted a continuity of the ventricular and pineal extracellular space. The pinealocytes of the deep pineal of the golden hamster project into the supraependymal recess of the third ventricle (Hewing, 1978). Furthermore, AVT, which has been localized in the stalk portion of the pineal of rats and cows (Benson *et al.*, 1976), is released into the cerebrospinal fluid of cats in response to intraventricular injections of saline solutions (Pavel and Coculescu, 1972).

Early work on the role of the pineal complex in hydromineral balance is equivocal. Pinelectomy or administration of pineal extracts to a variety of birds and mammals had no consistent effects on muscle hydration or blood levels of calcium, phosphorus, potassium, or mag-

nesium (Kitay and Altschule, 1954). However, Quay (1965b) noted that pinealectomized rats are deficient in their ability to maintain cerebral potassium content when fed a sodium-deficient diet. Chazov *et al.* (1973) have isolated a factor from the rat pineal which is reported to produce hyperkalemia when injected into rats. Clementi *et al.* (1965) have found that the antidiuresis and sodium retention resulting from reserpine administration is reversed by pinealectomy. Similarly, the rate of sodium transport across the small intestinal epithelium, is altered by administration of pineal extracts (Földvari *et al.*, 1962).

Some behavioral studies also indicate a possible role for the pineal complex in hydromineral balance. Pinealectomized rats prefer a 3% NaCl solution to fresh water (Krček *et al.*, 1975). This is accompanied by increased sodium retention. Neonatally pinealectomized rats exhibit a similar preference, but only while they are immature, losing it when they become adults (Reiter, 1977). Neonatal gonadectomy and pinealectomy combined result in the same response, but for a longer time (Reiter, 1977). These results should be taken cautiously, since the sham-operated animals have a significant increase in salt intake as well, although the response is less pronounced than in the pinealectomized animals.

There are also suggestions of a relationship between the pineal and calcium metabolism. Pinealectomized fish show defects in calcium metabolism, manifested by spinal deformities (Pflugfelder, 1956; Holmgren, 1959). Pinealectomy in rats promotes hyperplasia of the parafollicular cells of the thyroid, which are responsible for the secretion of thyrocalcitonin (Milne *et al.*, 1968). In a rather provocative series of experiments, Reiter and colleagues (Reiter and Morgan, 1972, 1973a,b) found that rats which have been parathyroidectomized, and then pinealectomized, quickly undergo violent convulsive seizures, frequently resulting in the death of the animal.

There are two proposed mechanisms for this curious response. Because, in a comparative study of four strains of rats, pinealectomy-parathyroidectomy resulted

in changes of levels of norepinephrine and serotonin in the central nervous system 8 hr after surgery, Philo and Reiter (1978) maintain that these alterations are the proximate events underlying the convulsions. However, the incidence of convulsions and the depletion of amines reveal no consistent pattern and cannot, in our opinion, support such a conclusion. It is interesting to note, nevertheless, that serotonin has been shown to ameliorate convulsive seizures in chicks (Hehman *et al.*, 1961) and melatonin, when applied directly to the brain, will alleviate the incidence and strength of artificially-induced epileptic foci in rats (Farriello *et al.*, 1976). The other obvious possibility is one involving a defect in calcium metabolism. In attempts to prevent or ameliorate the seizures by calcium replacement therapy, rats injected intraperitoneally with calcium gluconate immediately after pinealectomy showed the same predisposition to seizures as did the rats without calcium therapy (Reiter and Morgan, 1972), suggesting that calcium is not involved. However, such a conclusion would be premature in our view. First, in no case did the authors measure brain levels of calcium, a critical parameter in view of the hyperexcitability of nervous tissue under hypocalcemic conditions (Peach, 1975). The fact that the seizures seem to have sometimes been prompted by loud noises or flashes of light certainly suggests a hyperexcitable nature of the convulsing rats. Second, the regime of calcium replacement may not have been adequate to defend the brain against low blood calcium levels, particularly in rats with an impaired calcium control system. Despite the lack of an adequate explanation of mechanism, the experiments of Reiter and colleagues are perhaps the most dramatic examples of an involvement of the pineal complex in ionic regulation.

Hydromineral balance and thermoregulation have recently been postulated to interact with one another. Hayward (1970) noted that monkeys undergoing induced hypothermia suffer from "cold diuresis." Snellen (1972) has proposed a model whereby the regulated variable of body heat content (and not temperature

per se) is derived from the integration of hypothalamic temperature and ionic strength of the body fluid. This mechanism is believed to be responsible for the elevation of set-point typically seen during exercise and dehydration. Finally, Myers and Yaksh (1971) have proposed an ionic model for the set-point, which is determined by the ratio of sodium and calcium levels in the brain. The observation of Milne *et al.* (1969) that the size of the neuroglandular cells of the supraoptic nucleus of the rat increased subsequent to pinealectomy and cold exposure is interesting in this regard. De Vries (1972) noted a decrease in neurosecretory activity of the supraoptic nucleus following pinealectomy of rats. This effect was reversed by intrahypothalamic implants of the pineal.

Similar mechanisms may be operative in ectotherms as well. *Amphibolurus barbatus* elevate their panting thresholds when dehydrated (Parmenter and Heatwole, 1975) and lizards from arid habitats have greater head-body temperature differences and higher body temperatures (Webb *et al.*, 1972) than lizards from more mesic habitats. Sticklebacks (Garside *et al.*, 1977), mummichogs and banded killifish (Garside and Morrison, 1977) select higher temperatures in sea water than in fresh water. Metabolic rate of chuckawallas (*Sauromalus obesus*) is highly correlated with hydration state (Case, 1976), with dehydrated animals showing a reduced metabolic rate, particularly at higher temperatures. Balingier *et al.* (1970) reported that dehydrated animals regulate their body temperatures at lower levels than hydrated ones, which may be adaptive in reducing rates of respiratory water loss (Warburg, 1965; Templeton, 1970). Bury and Balgooyen (1977) have reported that California legless lizards (*Anniella pulchra*) select higher temperatures in a moist substrate than in a dry substrate. During hibernation and hypothermia, blood electrolytes of lizards undergo profound alterations (Haggag *et al.*, 1965; Raheem, 1975). Finally, drought conditions alter display frequencies in *Anolis* (Stamps, 1976), which could be expected to alter thermal behavior (Huey and Slatkin, 1976). However,

provocative though it might be, there is presently no evidence to suggest a pineal participation in these processes in ectotherms.

CONCLUSIONS

The evidence we have presented leads us to conclude that the primary locus of action of the pineal complex with respect to thermoregulation is the central nervous system. This may apply equally to both behavioral and physiological thermoregulatory control. Drawing upon the anatomical relations of the brains of several ectotherms, we present the following hypothetical scheme to explain these mechanisms (Fig. 3).

The parietal eye may exert an influence on behavioral thermoregulation through an action on the limbic system, possibly via the habenular nuclei. The area pretectalis may be a locus for parietal eye-pineal-lateral eye interaction, since it receives numerous projections from both the lateral eyes and the pineal organ, and is concerned with coordinating visual and motor information between the optic tectum, the cerebral cortex and the thalamus. The pineal tract may also project directly onto thermoregulatory centers such as the pre-optic nucleus, and the parietal eye may connect with this nucleus via the habenula. The possibility that these two components of the pineal complex (which are known to interact with each other) send separate tracts to the pre-optic nucleus may account for the divergent thermoregulatory effects observed following their removal. The suprachiasmatic nucleus may also participate in this scheme, in view of its known thermoregulatory action and its connection in mammals with the pineal gland. Finally, hypothalamic mechanisms for sensing and regulating body fluid osmolality and, in turn, body temperature, may be influenced by the pineal complex.

We have attempted to show that the pineal complex exerts an influence on thermoregulation in ectotherms through some kind of interaction with central nervous mechanisms. Perhaps other functions attributable to the pineal complex may be similarly controlled.

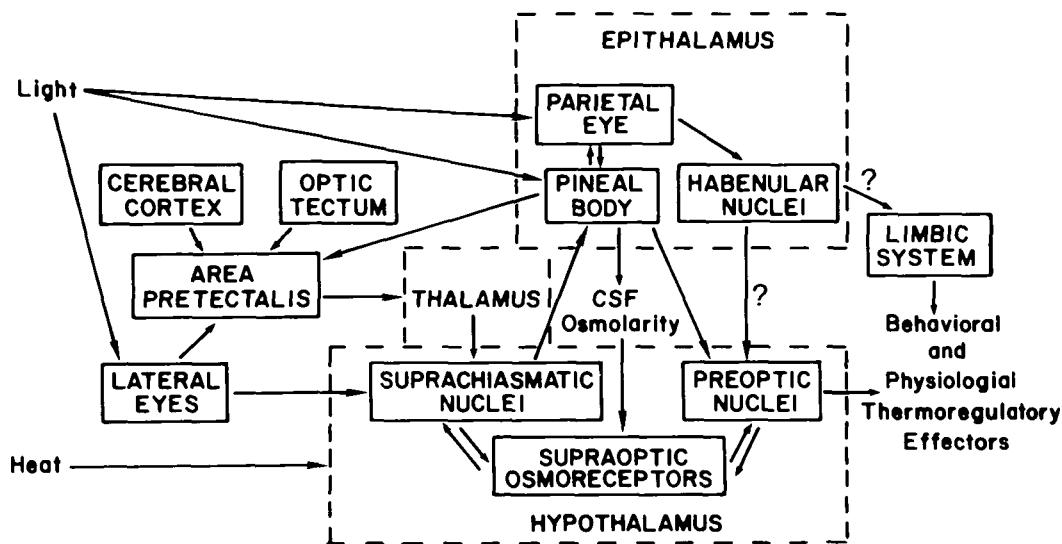


FIG. 3. Hypothetical scheme depicting the neuro-anatomical components influencing thermoregulation with which the pineal complex interacts. Some of

the anatomical associations are based on Pearson and Pearson (1976). See text for explanation.

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