

# Endocrine Considerations

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**Fig 19.1** | The European stork is a perfect example of birds learning to modify stressors.

## Stress

Many things can be stressful, including isolation,<sup>20</sup> weather change,<sup>101</sup> separation from mate, forced exercise,<sup>95</sup> fear,<sup>68</sup> starvation,<sup>67</sup> handling,<sup>60</sup> toxins and abnormal physical conditions, such as infection, trauma and pain.<sup>93</sup> Stress involves a cascade of physiologically adaptive responses. These responses can be demonstrated in altered behavior, such as aggression, escape attempts, vocalizations, changes in feeding and drinking, feather picking, repetitive movements and suppression of reproduction.<sup>79</sup> These varied physiological reactions do not constitute a uniform set of adaptive responses occurring in a predictable temporal fashion (**Fig 19.1**).<sup>93</sup> The most reliable response to stress is an elevation in circulating corticosterone levels.<sup>93,60</sup>

In a set of experiments, the temporal association of stress responses was determined. Juncos measured at handling and again in 30 minutes demonstrated a four-fold increase of corticosterone levels.<sup>60</sup> In chickens given a continuous infusion of adrenocorticotropic hormone (ACTH), the corticosterone response was within 2 hours. Other significant indicators of stress were elevation of glucose by 12 hours; increased liver weight along with increased hepatic lipid and decreased moisture by 18 hours; decreased relative weight of the spleen by 24 hours; elevated heterophil:lymphocyte ratio by 2 days; decreased body weight and relative weight of the bursa of Fabricius, as well as the weight of the thymus, by day 4; and decreased liver-soluble protein content by 12 days. Elevations in cholesterol, triglycerides, high-density lipoproteins, corticosterone and glucose were found to be reliable indicators of stress.<sup>111</sup> Polydipsia and polyuria were evident in chickens within 1 to 2 days of ACTH infusion.<sup>94</sup> Feed intake was slightly elevated over the

week of ACTH infusion; however, body weight was 20% lower 1 week postinfusion at the end of the experiment.<sup>94</sup> This was apparently due to a decrease in digestion of proteins, carbohydrates, dry matter and gross energy. Fat digestion was unaffected. Digestion was more affected than absorption and returned to control levels within 1 week. Post-ACTH infusion, as digestion returned to normal, absorption of nutrients was reduced. Losses of skeletal muscle from prolonged gluconeogenesis by catabolism of muscle protein from excess corticosteroids were not recovered by the end of the experiment (1 week).<sup>94</sup>

Migratory birds undergoing a prolonged fasting period did not demonstrate elevated corticosterone levels until fat stores were depleted to less than 5% of body mass. At that point, muscle catabolism occurred due to a moderate elevation of corticosteroids. Further secretion of corticosterone is inhibited when additional stressors are encountered. This may be a means to continue migration by using muscle protein for energy while finding a suitable landing area at which to feed.<sup>67</sup> Increased corticosterone levels coupled with decreased fat stores stimulate appetite and foraging.<sup>79</sup> In non-migratory birds forced to exercise, corticosterone levels were elevated proportionally as the intensity of the exercise increased.<sup>95</sup>

Corticosterone also affects various behaviors in birds. It can cause an inhibition of territoriality, rearing of young and behavior associated with breeding, without affecting luteinizing hormone or testosterone levels (see [Table 19.2](#)).<sup>126</sup> Severe stressors cause regression of the reproductive system in chicken hens.<sup>106</sup> Pharmacological doses of corticosterone can induce a preovulatory surge of luteinizing hormone and ovulation, whereas dexamethasone blocks ovulation, possibly because it suppresses corticosterone.<sup>106</sup>

Fear behaviors are seen with increased corticosterone levels; they may be attenuated with vitamin C supplementation.<sup>68</sup> Exogenous corticosterone induces protein catabolism and causes chickens to seek a high-protein diet.<sup>68</sup> Feather picking is associated with increased corticosterone levels.<sup>68</sup> This suggests that some feather-picking behavior may be a stress response to protein catabolism.

Glucocorticoids induce epinephrine synthesis while ACTH stimulates epinephrine and norepinephrine release.<sup>78,127</sup> These catecholamines augment, through  $\beta$ -adrenergic receptors, and suppress, through  $\alpha$ -adrenergic receptors, the plasma corticosterone responses to ACTH.<sup>96</sup> Increased epinephrine stimulates glycogenolysis, gluconeogenesis and lipogenesis. Norepinephrine helps maintain blood pressure.

Stress-induced immunomodulation has both beneficial and deleterious effects. Exogenous glucocorticoids or increased circulating levels of corticosterone cause involution of the thymus, bursa of Fabricius and spleen.<sup>35</sup> With early destruction of the bursa, the bursal hormones are not produced. This leads to a future stress hyporesponsiveness.<sup>24</sup> The composition of white blood cells moves toward an overall decrease in leukocytes, except heterophils, leading to an increased heterophil:lymphocyte ratio.<sup>45</sup> This decrease in leukocytes is partly due to the cells remaining in lymphoid organs.<sup>24</sup> A decrease in lymphocytes causes an overall suppression in antibody production.<sup>79</sup> In addition, glucocorticoids decrease inducible cellular cytotoxicity, lymphoproliferation, T-cell immunity, interleukin-2 and  $\gamma$ -interferon production.<sup>65</sup> Taken together, these responses may increase susceptibility to viral and other infectious agents.<sup>45</sup>

Lymphocytes themselves secrete ACTH and therefore boost circulating corticosterone levels following antigenic challenge.<sup>81</sup> The increase in corticosterone appears to cause a shift to increased T-helper cells and decreased T-suppressor cells in the spleen.<sup>81</sup> Macrophages are activated as they phagocytize an antigen. The activated macrophages secrete interleukin-1. Interleukin-1 increases secretion of corticotropin-releasing factor and ACTH, and activates lymphocytes, which increase production of ACTH.<sup>81,82</sup> Prolonged stress prior to antigenic stimulation may blunt the ACTH and interleukin-1 response.<sup>15</sup> The increased glucocorticoids cause the redistribution of circulating T-cells to secondary lymphoid tissues where antigens may be sequestered.<sup>81</sup>

Some amount of corticosterone is important in the immune response. Corticosteroids cause enhanced lymphocyte activity and the production of antibodies. Corticosteroids and ACTH later act in a negative feedback manner to regulate and control the process of antibody production by inhibiting lymphocyte activities and reducing the responsiveness to stimuli.<sup>82</sup> There is a significantly lower corticosterone response postantigenic stimuli in chicken strains that have autoimmune thyroiditis or avian scleroderma (another autoimmune disease).<sup>56</sup> This lack of response would attenuate the negative feedback of corticosterones on ACTH and may allow for a more pronounced immune response causing the autoimmune disease.

The administration of dexamethasone has been shown to depress ACTH and corticosterone for more than 24 hours.<sup>56</sup> In addition, both dexamethasone and prednisone decrease body weight gain, the number of natural killer cells, the number of lymphocytes in the spleen, production of interleukin-2 and  $\gamma$ -interferon by T-cells of the spleen.<sup>65</sup> These steroids also cause splenic atrophy,

increased body fat deposition, decreased percentage of immunoglobulin-A and immunoglobulin-M-bearing B-cells, decreased lymphoproliferation and increased susceptibility to *Eimeria* spp.<sup>65</sup>

The use of dexamethasone may cause more problems by not allowing for the natural effects of corticosterone. If steroid administration could be beneficial to the patient, the use of corticosterone or ACTH may be a better choice. When chickens infected with *Streptococcus faecalis* were given corticosterone at 30 mg/kg in feed in combination with ampicillin, the chickens were able to increase weight better than without corticosterone. Ampicillin alone did not alter the course of disease. Corticosterone alone was as good as the combination of ampicillin and corticosterone in most cases.<sup>48</sup> Another study demonstrated better resistance to *Escherichia coli* challenge exposure when corticosterone was given at 40 mg/kg in feed.<sup>49</sup> Pericarditis was reduced from 78% to 7%. No antibiotics were given. Resistance to respiratory infections was improved in pigeons given corticosterone, because of improved tracheal mucociliary transport.<sup>72</sup> Realizing that simply restraining a bird can elevate endogenous corticosterone tremendously, it may not be necessary to even treat with corticosterone, but simply to catch the bird several times.<sup>60</sup>

On the other hand, corticosterone depresses resistance to viral and *Mycoplasma gallisepticum* infections in poultry.<sup>46</sup> When chickens were given drugs to block the adrenal gland's production of corticosterone, fewer deaths and more effective cell-mediated immunity were seen to Newcastle disease and *Mycoplasma gallisepticum* infections. Additionally, a rapid remission of Marek's tumors was demonstrated.<sup>47</sup> Corticosterone and dexamethasone may decrease inhibin levels; this in turn increases follicle-stimulating hormone, which may cause follicle abnormalities.<sup>53</sup> Handling birds could conceivably exacerbate these diseases. Clinically, the use of mitotane (o,p'-DDD) has shown promise in controlling some neoplasias, viral infections and feather picking (G. Harrison, personal communication, 2002).

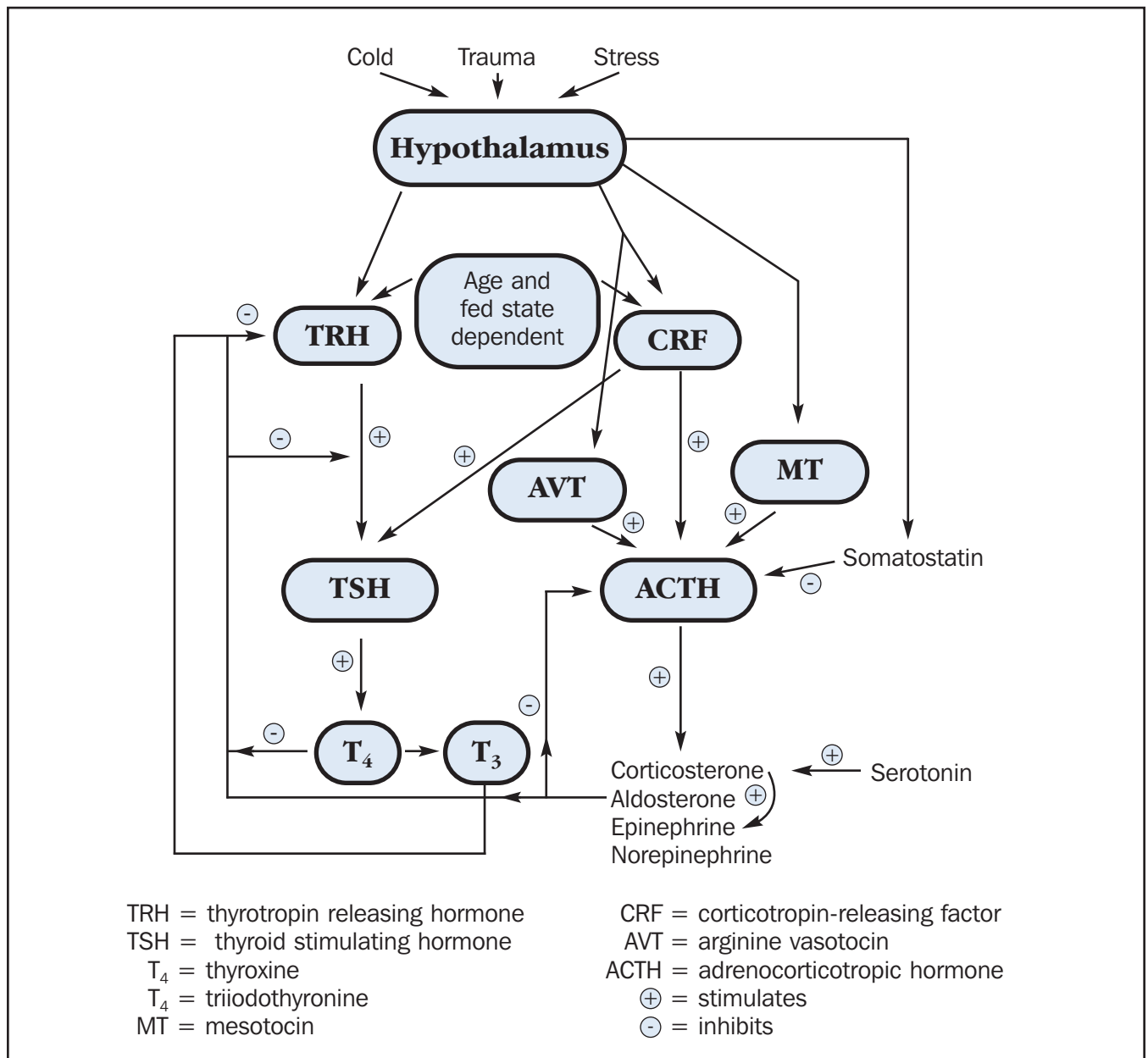
Many clinical problems may be due to a stressful environment (i.e., fatty liver disease, feather picking and reproductive abnormalities). Many patients present with liver disease. In these cases, the liver may not be able to metabolize natural or exogenous glucocorticoids. Appropriate nutrition is imperative to the health of our patients; however, nutrition and other therapies cannot override conditions brought on by chronic stress. The best therapy for many of the diseases we encounter should be directed toward the psychological well-being of our patients (Figs 19.2, 19.3 and Tables 19.1, 19.2).

**Table 19.1 | Causes of Corticosterone Elevation**

- Immobilization
- Protein restriction
- Starvation
- Fear
- Pain
- Increase in plasma osmolality
- Oviposition
- Prostaglandins
- Low 3,5,3'-triiodothyronine (T<sub>3</sub>)
- Depressed liver metabolism of corticosterone
- Growth hormone
- Angiotensin II (See Fig 19.8)
- Prolactin
- Parathyroid hormone
- Catecholamines
- Serotonin
- Vasoactive intestinal peptide
- Activated immune cells
- Corticotropin-releasing factor
- Arginine vasotocin
- Mesotocin
- Adrenocorticotropin hormone (ACTH)
- Melatonin
- Progesterone
- Opioids
- Exercise

**Table 19.2 | Effects of Corticosterone**

Increases	Decreases
<ul style="list-style-type: none"> <li>• Feeding behavior</li> <li>• Fat stores</li> <li>• Gastric transit time</li> <li>• Muscle catabolism</li> <li>• Glucose</li> <li>• Insulin (counteracted by down regulation of liver receptors, thus causing insulin resistance)</li> <li>• Involution of the thymus, bursa and spleen</li> <li>• Heterophil: Lymphocyte ratio</li> <li>• Trapping of leukocytes in secondary lymphoid organs</li> <li>• Susceptibility to viral infections, coccidiosis and <i>Mycoplasma</i> spp.</li> <li>• Resistance to some bacteria</li> <li>• Tracheal mucociliary clearance</li> <li>• Fearfulness</li> <li>• Oral stereotypic behavior (feather picking, polydipsia, pecking)</li> <li>• Protein eating</li> <li>• Sodium reabsorption in renal tubules</li> <li>• Level of sodium-linked water uptake across the intestinal and hindgut mucosa</li> <li>• Catecholamines</li> <li>• Cholesterol</li> <li>• Triglycerides</li> <li>• High-density lipoproteins</li> <li>• Liver size (due to hepatic lipogenesis)</li> <li>• Salt gland secretion of NaCl</li> <li>• Lipolysis from adipocytes</li> <li>• Free fatty acids</li> <li>• Luteinizing hormone</li> <li>• Glomerular filtration rate</li> </ul>	<ul style="list-style-type: none"> <li>• T<sub>3</sub></li> <li>• Territoriality</li> <li>• Growth</li> <li>• Body weight</li> <li>• Circulating WBC</li> <li>• Lymphoproliferation</li> <li>• Interleukin-2</li> <li>• <math>\gamma</math>-interferon</li> <li>• Inducible cellular cytotoxicity</li> <li>• Cell-mediated immunity</li> <li>• Antibody response</li> <li>• Potassium excretion in renal tubules</li> <li>• Absorption and digestion of nutrients</li> </ul>



**Fig 19.2** | Hypothalamo-Pituitary-Adrenal Axis Hormones

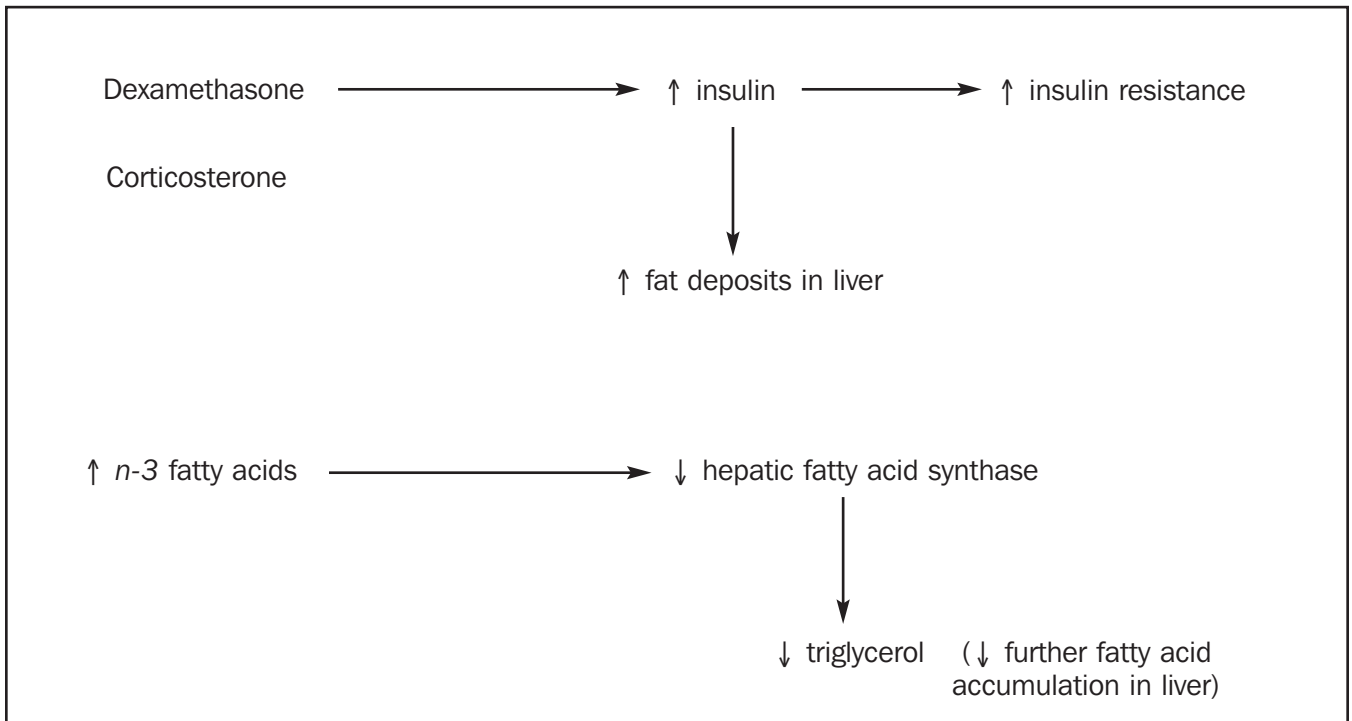
## Growth

Growth primarily involves cell proliferation, but also may result from cell hypertrophy. The primary hormones involved with growth are: growth hormone (GH), triiodothyronine (T<sub>3</sub>) and insulin-like growth factor-1 (IGF-1). Contradictions in the literature due to variable experimental designs are exacerbated by the different actions of various hormones, depending on age and nutritional status. [Fig 19.4](#) demonstrates an overview of hormonal interactions. [Tables 19.3-19.5](#) delineate what effects these hormones have on growth and body condition.

The reader should be aware that all available growth studies look at growth in poultry. There may be some undiscovered variations among other species of birds.

There are many hormones active during embryogenesis. Insulin and insulin-like growth factors are reported to stimulate embryonic metabolism, growth and differentiation.<sup>41</sup> Some growth factors appear to have more specific actions in embryogenesis, though many seem to have synergistic activity with IGF-1. [Table 19.6](#) lists some of the growth factors and their respective actions.

As poultry moves into its rapidly growing phase at 3 to 4 weeks posthatch, GH and IGF-1 levels peak and then gradually decline to their minimum concentrations at about 8 weeks posthatch. During this period of rapid growth, administration of exogenous GH or IGF-1 demonstrates no effect on growth rate.<sup>22,85</sup> As endogenous nutrient partitioning is shifted toward greater fat deposition, as seen with increasing age and cessation of



**Fig 19.3** | Fatty Liver

growth, exogenous GH is effective in decreasing fat and increasing muscle formation.<sup>85</sup> GH in adult birds is a potent lipolytic hormone and also increases blood glucose levels.<sup>22</sup> There does not appear to be a diabetogenic effect, as seen in humans administered GH, possibly due to increased sensitivity of peripheral insulin receptors. GH also can block glucagon-induced lipolysis resulting in antilipolytic activity. Exogenous GH, in 8- to 9-week posthatch poultry, reduced feed intake and body weight gain.<sup>119</sup> The reduction of feed intake may be secondary to GH's reduction of neuropeptide Y protein, a potent appetite stimulant.<sup>119</sup>

In growing birds, GH decreases  $T_3$  degradation resulting in elevated  $T_3$  concentrations.<sup>30</sup> The effect of  $T_3$  is developmentally regulated. Exogenous GH produces a hyperthyroid response in late embryogenesis, newly hatched and adult birds.<sup>29,75</sup> This effect disappears during the rapid growth phase, most likely due to masking by high endogenous GH and  $T_3$  levels.<sup>30,119</sup> In mammals, GH must bind to two sites of the receptor, similar to antibody-antigen cross-bridging. Therefore, high levels of GH may block signal transduction.<sup>37</sup>

Growth hormone receptors and growth hormone-binding proteins also may play an important part in age-related actions. In young birds, growth hormone receptors are low, and GH and growth hormone-binding protein levels are high. Exogenous GH would have little to no effect. In adult chickens, growth hormone receptors are elevated and GH is low. In this case, exogenous GH may initially have stimulatory effects; however, at some

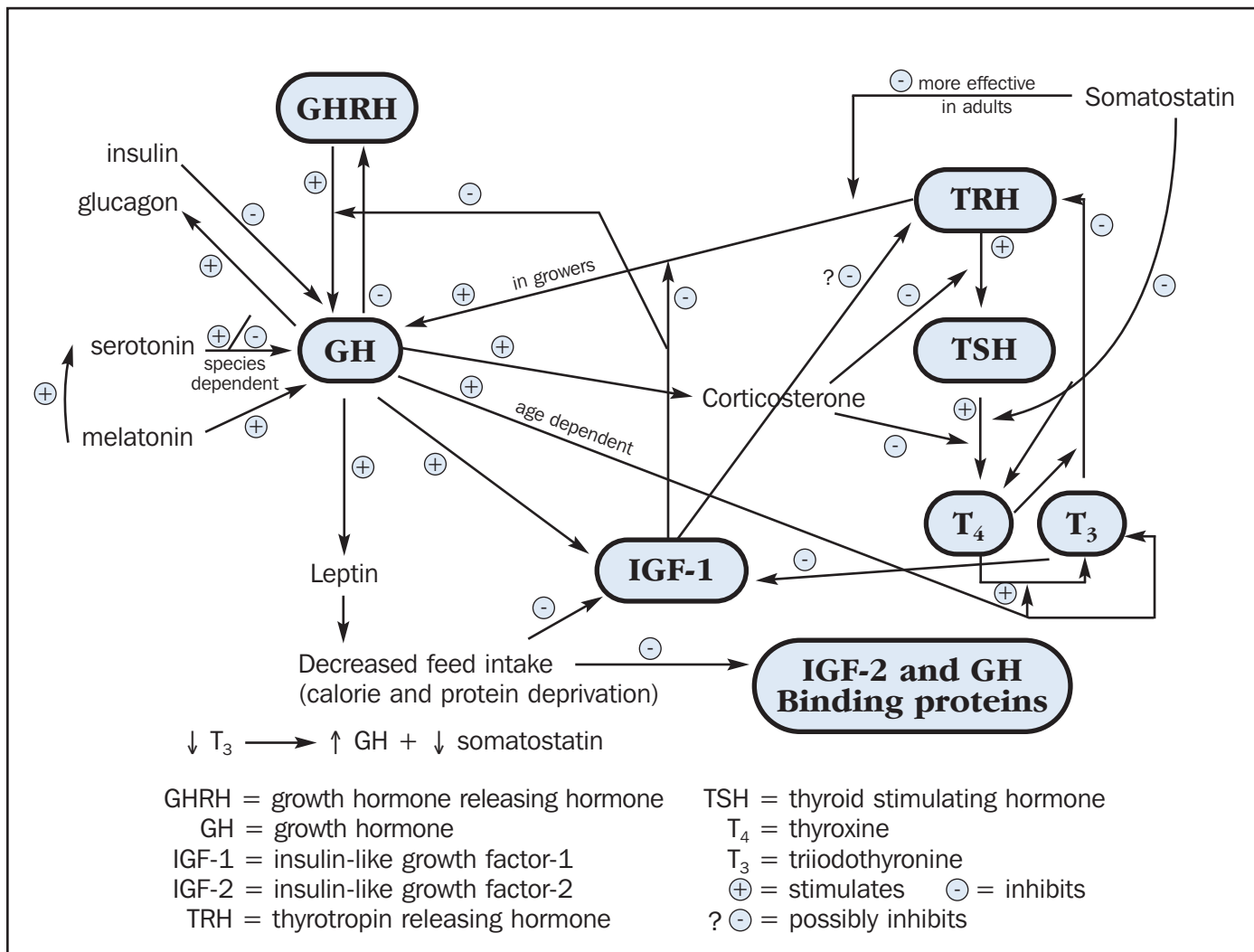
point, the excess GH may be bound by increased levels of growth hormone-binding protein and GH-induced down regulation of growth hormone receptors.<sup>53</sup> Binding of GH may keep it from attaching to receptors, but also may prolong its half-life.<sup>53</sup>

$\beta$ -adrenergic receptor agonists, epinephrine and norepinephrine also appear to have a significant role in growth and body composition. When clenbuterol ( $\beta$ -adrenergic receptor agonist) was given orally, growing chickens decreased their fat mass, while increasing their muscle mass, weight gain and gain-to-feed-intake ratio.<sup>85</sup> These changes could be from a direct effect on muscle and adipose tissue, modification of blood flow, central nervous system control of feed intake and/or action of other hormones (ie,  $T_3$ , corticosterone, insulin, GH).

The majority of information on growth in birds is still quite controversial, with many questions left unanswered. Those answers found in poultry may have little to offer other species of birds.

## Thyroid

Thyroid hormones influence or are influenced by almost all physiological, environmental and nutritional parameters. When interpreting the literature, it is important to correlate the age of bird with the actual dose of drugs used in the experimental design to interpret the data correctly.



**Fig 19.4** | Growth Hormone

**Table 19.3** | Growth Hormone Effects

Increases	No Effect	Decreases
<ul style="list-style-type: none"> <li>• Differentiation and proliferation of target cells (i.e., muscle)</li> <li>• Glucose</li> <li>• Fat in growing birds</li> <li>• Insulin-like growth factor-1 in selected muscles of adults</li> <li>• Exogenous GH: Fat birds between 3-5 weeks of age, lipolytic Other birds lipogenic Increase insulin and tryglycerides at 24 days of age Increase tibia length between 2-24 days of age In adult birds, large increase in T<sub>3</sub></li> <li>• Large increase of T<sub>3</sub> at late embryo early hatch</li> <li>• Conversion of thyroxine (T<sub>4</sub>) to triiodothyronine (T<sub>3</sub>)</li> <li>• Moderate increase of T<sub>3</sub> at growth stage due to decreased degradation of T<sub>3</sub></li> </ul>	<ul style="list-style-type: none"> <li>• Exogenous GH 2-24 days post hatch - no effect on growth, feed intake, carcass protein, 8-9 weeks post- hatch - no effect on IGF-1 levels</li> </ul>	<ul style="list-style-type: none"> <li>• Fat in adults</li> <li>• Neuropeptide Y</li> <li>• Feed intake at 8-9 weeks post-hatch</li> <li>• Muscle growth at 8-9 weeks old</li> <li>• Hypothalamic epinephrine</li> <li>• Degradation of T<sub>3</sub></li> </ul>

**Table 19.4 | Effects of Insulin-like Growth Factor-1 (IGF-1)**

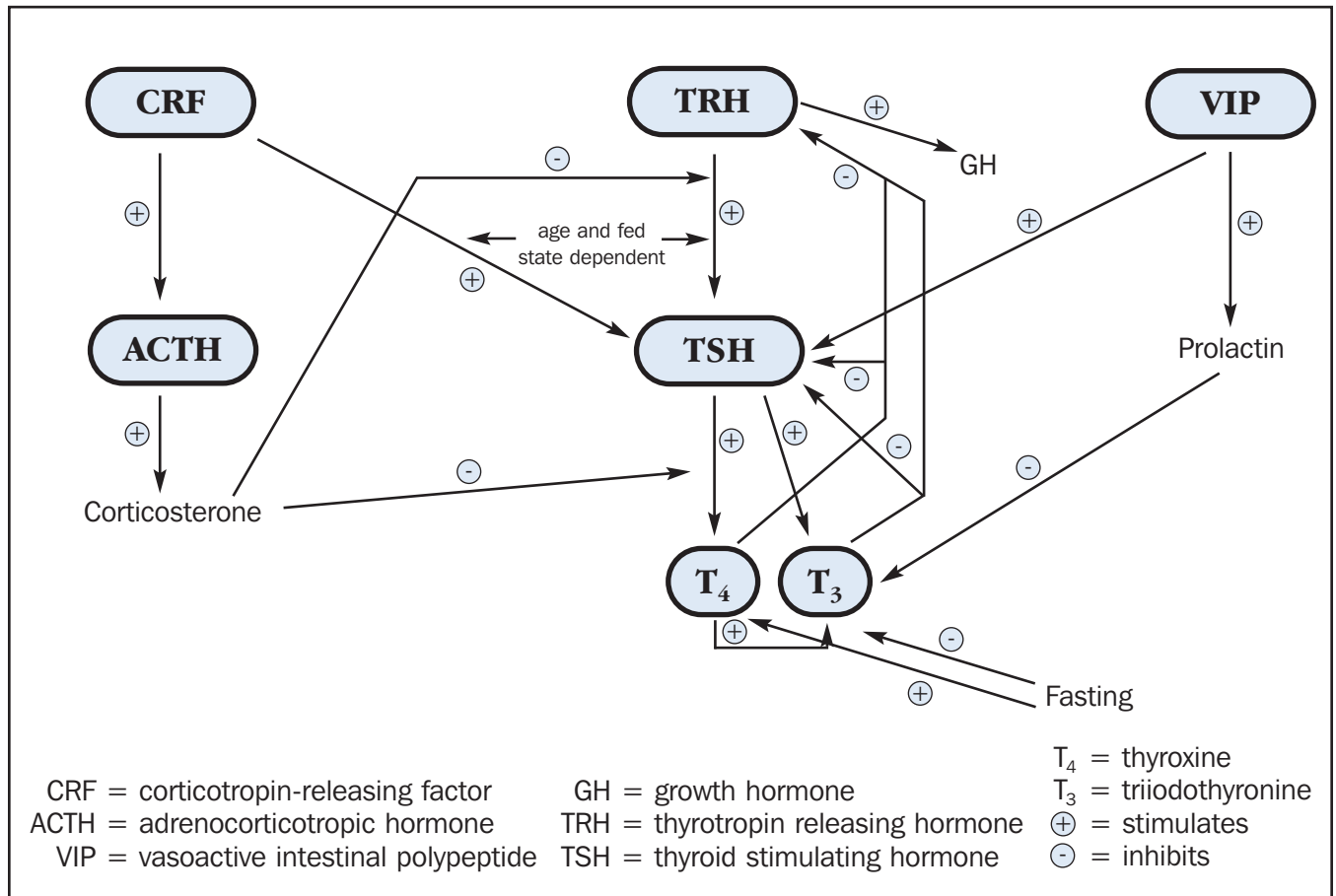
Increases	No Effect	Decreases
<ul style="list-style-type: none"> <li>• Metabolism, growth, differentiation, organogenesis of the embryo</li> <li>• Fat in growing poultry</li> <li>• Glucose uptake</li> <li>• Amino acid uptake and protein synthesis</li> <li>• Inhibition of protein degradation</li> <li>• Proliferation of turkey and chicken myoblasts</li> <li>• Peripheral tissue sensitivity to insulin</li> <li>• Exogenous IGF-1 increases heart weight and muscle breakdown in 3-week-old chickens</li> </ul>	<ul style="list-style-type: none"> <li>• Exogenous IGF-1 has no effect on growth or protein synthesis rate</li> </ul>	<ul style="list-style-type: none"> <li>• Insulin</li> <li>• Insulin:glucagon ratio</li> <li>• GH lipolysis in growing birds</li> <li>• Muscle growth in chickens greater than 8 weeks posthatch</li> <li>• Muscle weight in 3-week-old chickens</li> <li>• Glucose</li> </ul>

**Table 19.5 | Effects of Triiodothyronine (T<sub>3</sub>) on Growth**

Increases/Stimulates	Decreases	Low Levels of T <sub>3</sub>
<ul style="list-style-type: none"> <li>• Accretion of muscle protein during growth</li> <li>• Muscle mass and feather development in growers</li> </ul>	<ul style="list-style-type: none"> <li>• GH</li> <li>• IGF-1: may be age-dependent at low dose</li> <li>• Fat in growing birds</li> <li>• Muscle mass due to decreased protein synthesis in non-growing birds</li> </ul>	<ul style="list-style-type: none"> <li>• Increase GH</li> <li>• Decrease skeletal, muscle and feather development in growers</li> <li>• Decrease cardiac ventricle and pectoral mass in growers</li> </ul>

**Table 19.6 | Growth Factors Involved with Embryogenesis**

Increases/Stimulates	Factors
Insulin-like Growth Factors (IGF)	• IGF-1 most important (see Table 19.4)
Epidermal Growth Factor (EGF)	• With IGF-1 and Fibroblast Growth Factor (FGF) stimulates proliferation of heart mesenchymal cells
Fibroblast Growth Factor (FGF)	See EGF Stimulates: <ul style="list-style-type: none"> <li>• Muscle and bone development</li> <li>• Differentiation of blastoderm cells into erythropoietic cells</li> <li>• Proliferation of preadiposites</li> <li>• Proliferation of chondrocytes with transforming growth factor-<math>\beta</math> (TGF-<math>\beta</math>)</li> <li>• With IGF-1 proliferation of chicken myoblasts</li> </ul>
Nerve Growth Factor (NGF)	• Neural development
Transforming Growth Factor- $\beta$ (TGF- $\beta$ )	Includes several TGF- $\beta$ s, e.g.: <ul style="list-style-type: none"> <li>• Inhibin/Activin subunits</li> <li>• Bone Morphogenic Protein-4 (BMP-4)</li> <li>• Glial Cell-Derived Nerve Growth Factor (GDNF)</li> <li>• Muellierian Inhibitory Substance (MIS)</li> <li>• Platelet-Derived Growth Factor (PDGF)</li> </ul>
TGF- $\beta$	Decreases: <ul style="list-style-type: none"> <li>• DNA synthesis and melanocyte formation in neural crest cells</li> <li>• Collagen production</li> </ul> Stimulates: <ul style="list-style-type: none"> <li>• Expression of fibronectin</li> <li>• Proliferation of chondrocytes with FGF and adiposites</li> <li>• Limb formation</li> <li>• Synthesis of non-collagen protein</li> <li>• Muscle cell differentiation</li> </ul>
Inhibin	<ul style="list-style-type: none"> <li>• Blocks release of follicle-stimulating hormone (FSH)</li> <li>• With activin may play an antagonistic role in paracrine regulation of embryonic gonadal steroidogenesis</li> </ul>
Activin	See Inhibin <ul style="list-style-type: none"> <li>• Stimulates release of FSH</li> <li>• Determines right and left asymmetry</li> </ul>
Bone Morphogenic Protein-4 (BMP-4)	Stimulates: <ul style="list-style-type: none"> <li>• Osteoinduction</li> <li>• Gastrulation</li> <li>• Neural crest cell apoptosis</li> </ul>
Glial Cell-Derived Nerve Growth Factor (GDNF)	• Increase survival of motor neurons by reducing programmed apoptosis
Muellerian Inhibitory Substance (MIS)	• Muellierian duct regression in males
Platelet-Derived Growth Factor (PDGF)	<ul style="list-style-type: none"> <li>• Stimulates transformation of chicken myoblasts</li> <li>• Inhibits differentiation</li> </ul>



**Fig 19.5** | Thyroid Hormones

In chickens of all ages, thyroid stimulating hormone (TSH) stimulates the release of predominately thyroxine (T<sub>4</sub>) and lesser amounts of triiodothyronine (T<sub>3</sub>). Age changes the mechanisms controlling TSH release and the peripheral productions of T<sub>3</sub>. In the embryo, corticotropin releasing factor and thyrotropin releasing hormone may control TSH release.<sup>105</sup> Thyrotropin releasing hormone stimulates the release of growth hormone (GH), which inhibits degradation of T<sub>3</sub> through the growing phase (see Growth section, this chapter). Growing chickens respond differently to thyrotropin releasing hormone when fasted. During a 1-day fast, thyrotroph cells increase their sensitivity to thyrotropin releasing hormone and corticotropin releasing factor. However, these cells do not release TSH because fasting induces a decrease in thyrotropin releasing hormone secreted by the hypothalamus.<sup>40</sup> Fasting also increases corticosterone levels, which inhibit secretion of thyrotropin releasing hormone and, thus, TSH release. This was demonstrated in chickens with one injection of 40 μg of corticosterone.<sup>40</sup>

As chickens mature, they are less responsive to thyrotropin-releasing hormone effects on TSH. TSH appears to be more sensitive to circulating concentrations of T<sub>3</sub>

than T<sub>4</sub>.<sup>105</sup> **Figs 19.2, 19.4 and 19.5** elucidate some of the pathways involved in thyroid regulation.

## PHOTOSTIMULATION

Increasing day lengths induce photostimulated reproductive activity and postnuptial molt. It has been suggested that this onset of photostimulation combined with endogenous thyroid hormones organize the events of seasonality.<sup>124</sup> When American tree sparrows (*Spizella arborea*) were moved from short to long days, T<sub>4</sub> along with circulating luteinizing hormone increased early during photostimulation, peaking between weeks 1 and 2. This was followed by luteinizing hormone-releasing hormone and luteinizing hormone peaking between weeks 2 and 4. By week 6, gonad development was near maximum. Thyroid activity peaked during copulation.<sup>25,97,123,124</sup> The postnuptial molt began at week 9 and ended by week 18.<sup>97</sup> A series of experiments on intact and variably timed thyroidectomies concluded that thyroid-dependent gonadal growth was programmed during the first 7 days of photostimulation. Photorefractoriness and initiation of molt were programmed between 7 and 21 days of photostimulation.<sup>53</sup> T<sub>3</sub> failed to program birds for these events. This suggests that T<sub>4</sub> directly or non-T<sub>3</sub> metabolites are the responsible hormones.<sup>124</sup>



## Cases

Most reports of thyroid conditions in birds involved those genetically designed for hypothyroidism (ie, chickens of the obese strain, and white carneau pigeons). The only case of confirmed hypothyroidism in a psittacine was reported in a scarlet macaw. This report described contour feather loss, no indication of feather regrowth and excess subcutaneous fat. Skin biopsies demonstrated a catabolic state, a finding inconsistent with hypothyroid cases. A TSH stimulation test confirmed that the bird was hypothyroid. The bird responded to thyroid hormone replacement in the water at 0.015 mg/kg BID, which was later reduced to daily therapy.<sup>89</sup> It was not clear if this was a lifelong therapy or was discontinued after the resolution of signs. If the bird was taken off thyroid medication and remained euthyroid, it could have been due to a resolving thyroiditis, stressful environment and/or inadequate nutrition.

Goiter has often been associated with iodine-deficient budgerigars. Another incidence of goiters was reported in a goose flock of 2300 birds.<sup>66</sup> Though geese feeding on rapeseed meal develop goiters, rapeseed was not part of this flock's ration. The major pathological findings were increased relative thyroid weight, fat accumulation, and retarded growth and plumage development. One group of birds was treated with iodine and another group was not. After 55 days, both groups improved. A hunt for possible goitrogenic substance was not successful.<sup>66</sup> The two study groups were put in less dense environments. This may have resulted in less stress, therefore less circulating corticosterone and less suppression of thyroid activity. A recent report found a disproportional number of macaws with hyperplastic goiter. Seventy-five percent of these cases were in blue and gold macaws (*Ara araucana*). The cause was not determined.<sup>104</sup>

Avian muscular dystrophy in chickens has been treated by thyroidectomy. Maintenance of low T<sub>3</sub> plasma levels with exogenous T<sub>3</sub> replacement alleviated signs attributable to the disease. These chicks demonstrated a large increase in T<sub>3</sub> maximum binding capacity in dystrophic muscles.<sup>73</sup>

Cysts, adenomas and adenocarcinomas have been reported infrequently in several genera of birds. As intensive breeding and pollution with hormonally disruptive chemicals increase, thyroid disease may be reported more frequently.

## TESTING

Most available thyroid tests are designed for humans or dogs. These tests are not usually able to detect the relatively low concentrations of T<sub>4</sub> in the avian patient.<sup>43</sup> When testing for thyroid hormones, it is important that

the test be validated for birds. The necessity of incubating serum samples with proteolytic enzymes, and then precipitating with ethanol to avoid binding proteins in the serum has been demonstrated.<sup>44</sup> Without these extra steps, the test will be inaccurate.<sup>45</sup> Another source of difficulty is the lack of good reference ranges. With so many variables capable of altering thyroid levels, it is important that those birds used for reference ranges be fed, housed and cared for optimally.

T<sub>4</sub> blood levels fluctuate normally during a 24-hour cycle, generally being higher in the night and during a fast.<sup>84</sup> To measure T<sub>4</sub> activity more accurately, a TSH stimulation test is required. Recently, a stimulation test in several genera of birds has been developed using synthetic human thyroid stimulating hormone.<sup>44</sup> It was found that a 0-hour baseline blood sample, TSH at 1.0 IU/kg IM and a second blood sample in 6 hours gave consistent results.

# Pancreas

## ENDOCRINE-GLUCOSE REGULATION

Glucose regulation is the primary endocrine function of the pancreas. Effective glucose metabolism also maintains normal protein and lipid metabolism. Neural, retinal and adrenal tissues require glucose. The avian liver is the primary source of glucose to the plasma by its interaction with the pancreas. The pancreas releases the proper ratio of insulin and glucagon. The combination of hormones and absorbed nutrients work together in the liver to release products of digestion in dynamic response to the bird's needs. After a bird feeds, plasma glucose and amino acid levels increase causing insulin release from the pancreatic B-cells. Insulin aids hepatic enzymes in glycogenesis. In the liver, protein synthesis and lipogenesis produce approximately 95% of lipids through insulin stimulation. Thyroid hormones augment the process. Insulin is therefore an anabolic hormone.

In the fasting state, the liver is important for retrieving energy sources and making them available. With lower blood glucose concentrations, insulin levels are low and glucagon levels are high. At the liver, glucagon causes lipolysis, glycogenolysis and stimulates gluconeogenesis.<sup>112</sup> Glucagon is therefore a catabolic hormone. The glucagon/insulin responses to food intake maintain stable blood glucose levels. A variety of species of birds demonstrate only small declines during prolonged (5 to 7 days) fasts.<sup>114</sup> We have seen emaciated birds with only slightly decreased blood glucose. A study in migrating garden warblers (*Sylvia borin*) found that glucose utilization rate is reduced as food deprivation continues to

about 7 days. These experiments suggest that during migration, a period of prolonged fasting, glucose utilization may be supplanted by oxidation of fatty acids.<sup>113</sup>

Adipose, kidney and muscle tissues each play a role in maintaining energy sources. The kidney can provide up to 30% of glucose by gluconeogenesis. Adipose tissue is important in providing lipids through lipolysis.<sup>39</sup> During a catabolic state, muscle tissue itself may be broken down (see Stress section, this chapter).

Cholecystokinin, glucagon and a mixture of absorbed amino acids strongly stimulate, whereas glucose only weakly stimulates insulin release. Insulin enhances protein synthesis and is required for embryonic myogenesis and muscle structural proteins in adult birds. At the level of the muscles and adipocytes, insulin increases glucose transport carriers. These proteins increase the transport of free glucose from the extracellular fluid across the cell membrane. Insulin aids transport of amino acids into cells. Insulin, or its hypoglycemic effect, causes glucagon release and results in an increase in free fatty acids. Therefore, insulin's overall effects are to remove glucose and amino acids from circulation, increase lipidemia and inhibit gluconeogenesis.

Free fatty acids and cholecystokinin stimulate glucagon release from the pancreatic A-cells. In contrast to other avian species, ducks also release glucagon in response to insulin and somatostatin. Glucose inhibits glucagon release. Glucagon suppresses leptin, a hormone that suppresses appetite, T<sub>3</sub> and T<sub>4</sub>.<sup>3,83</sup>

Somatostatin controls the ratio of insulin to glucagon released from the pancreas. Islet cells appear to be contiguous with each other and share intra-islet extracellular fluid. Somatostatin from pancreatic D-cells inhibits secretion from all other islet cells. Glucagon is the most sensitive and pancreatic polypeptides are the least sensitive to somatostatin. At the level of the gut, somatostatin decreases intestinal absorption of glucose and lipids. This hormone's actions allow a dynamic regulation of gluco-homeostasis.

Absorbed nutrients stimulate D-cell somatostatin and A-cell glucagon activity. Increased glucose and amino acids stimulate B-cells (insulin) whereas glucose depresses A-cells (glucagon). F-cells (pancreatic peptides) are stimulated by cholecystokinin, secretin, gastrin and absorbed amino acids. In summary, A-cells stimulate B- and D-cells; D-cells inhibit A-, B- and F-cells. Pancreatic polypeptides from the F-cells are glycogenolytic without producing hyperglycemia. They also act to lower plasma glycerol, cholesterol, fatty acids and apolipoproteins, while increasing triglyceride levels.<sup>105</sup> Pancreatic polypeptides inhibit gut motility and gut, exocrine pancreatic

and gallbladder secretions. They also are antilipolytic and induce satiety via the central nervous system.<sup>55</sup>

## EXOCRINE

Exocrine pancreatic secretions include trypsinogen, chymotrypsinogen, trypsin inhibitor, procarboxypeptidase, amylase and lipase. These enzymes are released into the duodenum and, along with gut peptides, further digestion. Trypsinogen and chymotrypsinogen are secreted in an inactive form so as not to induce autodigestion. Enterokinase from the gut activates trypsinogen to trypsin. Trypsin, in turn, cleaves chymotrypsinogen to chymotrypsin.

Factors influencing exocrine pancreatic enzyme secretion include the following: feeding, distention of the proventriculus with peptones, gastrin-releasing peptides, increased cholecystokinin, vasoactive intestinal peptide, neurotensin, secretin, hydrochloric acid, vagus innervation and cholinergic agents.<sup>23,59,74,100,118</sup>

Cholecystokinin influences the enzymatic content of pancreatic secretions except amylase.<sup>34,86</sup> Secretin, and to a larger extent vasoactive intestinal peptide, increase the aqueous component of pancreatic juices. Neurotensin increases lipase and depresses amylase secretion. Ingestion of lipids causes neurotensin release from intestinal stores.<sup>33</sup> Diets rich in carbohydrates increase amylase, fats increase lipase, and protein increases chymotrypsin activity in pancreatic secretions.<sup>19,64</sup> The release of some of the islet hormones occurs before nutrients are even absorbed into the bloodstream, allowing for rapid adjustments to maintain homeostasis.

## Exocrine Pancreatic Insufficiency

Exocrine pancreatic insufficiency in birds has been suggested by the observation of undigested food in the feces, voluminous foul-smelling droppings, weight loss and failure to thrive. With many cases of psittacine proventricular dilation presenting similarly, appropriate biopsies may be indicated to assist in diagnosis. Pancreatic insufficiency has been reported as a secondary effect of a pancreatic adenocarcinoma.<sup>98</sup> This yellow-naped Amazon (*Amazona ochrocephala auropalliata*) was presented with a 3-month history of weight loss and voluminous foul-smelling droppings. Confirmation of pancreatic insufficiency was made from fecal tests positive for neutral and split fats and negative for trypsin. In addition, no elevation in blood triglyceride levels occurred with oral corn oil administration until the oil was mixed with pancreatic enzymes. The pancreatic adenocarcinoma was found on necropsy.<sup>98</sup>

Another case in a macaw was reported with feces containing starch and fat. The bird's feces returned to nor-

mal with the addition of trypsin to the food. When trypsin was discontinued 6 weeks later, the feces remained normal.<sup>90</sup> A slightly acidic diet rich in peptones should increase pancreatic exocrine secretions. This may prove a useful therapeutic adjunct to the addition of pancreatic enzymes to the food.

### Diabetes Mellitus and Pancreatitis

In most granivorous birds, hyperglycemia occurs with normal insulin and increased glucagon levels, however, some birds have been documented with low insulin levels.<sup>90</sup> Clinical signs attributable to hyperglycemia are severe polyuria, polydipsia, increased appetite, and weight loss.<sup>90</sup> Often there is a history of obesity and poor nutrition. Hyperglycemia may be secondary to other diseases and often resolves when the underlying disease is treated. Hyperglycemia in obese psittacines has responded to low-fat diets and weight loss. Obese Quaker parakeets (*Myiopsitta monachus*) have been found to have pancreatic necrosis.<sup>71</sup> Those that survive have pancreatic insufficiency. A number of viruses, such as herpes, pox and polyomavirus, may cause pancreatic pathology.<sup>42</sup> Birds on certain drugs (eg, medroxyprogesterone) have shown signs of hyperglycemia.

It has been suggested that an amylase greater than 2000 IU/L is diagnostic for pancreatitis. Lower values of amylase may be more indicative of renal disease. Chronic stress causes chronic hyperglycemia with increased insulin levels and resultant insulin resistance. To evaluate a bird with hyperglycemia it is important to keep environmental stressors to a minimum. Evaluating the home situation and diet may indicate stress and/or nutritional issues. If possible, glucagon, insulin and amylase should be evaluated along with evidence of persistent hyperglycemia. A urine dipstick in normal birds usually demonstrates negative or trace glucose. Radiographs and fecal Gram's stains may aid in the search for any underlying diseases.

### Treatment

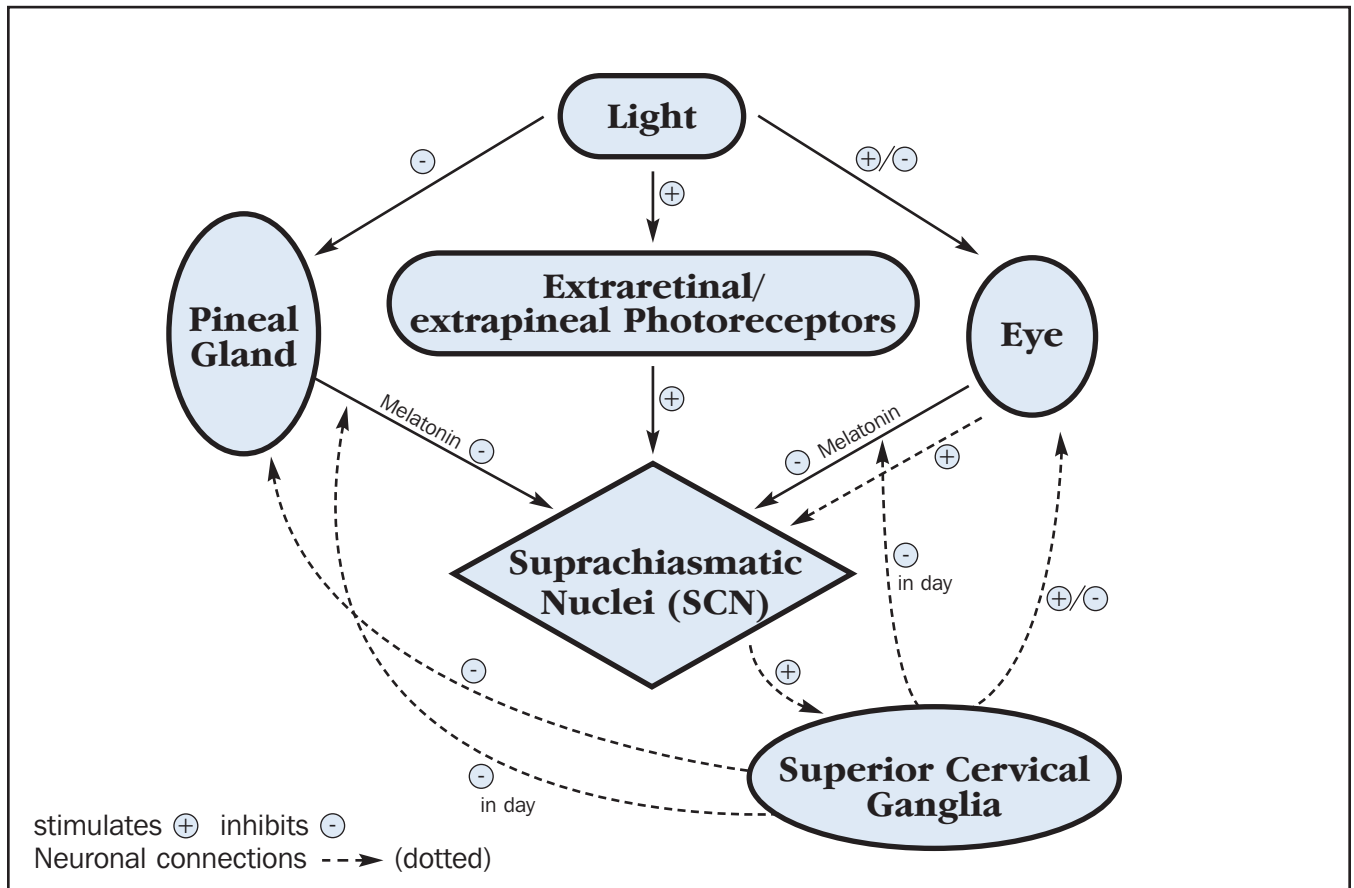
If insulin levels are depressed, the bird may respond to exogenous insulin. Insulin protocols are extrapolated from other species and are carried out in much the same way as in mammals. Somatostatin was tried in a sulfur-breasted toucan (*Ramphastus sulfuratus*) at 3 µg/kg SC BID. The bird improved clinically, but died acutely after 4 months. The body was not presented for necropsy. During therapy, the bird maintained high glucose (>1300 mg/dl) and glucagon (>3100 pg/ml) levels. It would be interesting to evaluate higher doses of somatostatin.<sup>71</sup> If glucagon is elevated, it would be interesting to try antiglucagon serum. When anti-insulin serum was used in chickens, glucose became extremely elevated.<sup>107</sup>

Oral medications may have promise. Glipizide, a drug that increases insulin release from  $\beta$ -cells, has been used successfully in some cases at 1 mg/kg PO BID (Echols, personal communication). Other oral medications that may be tried include thiazolidinediones, which enhance peripheral insulin sensitivity, and  $\alpha$  glucosidase inhibitors, which delay glucose absorption from the gut. Chicks with dexamethasone-induced hypocorticalism demonstrated increased insulin sensitivity and attenuated glucagon responsiveness.<sup>70</sup>

## Pineal Gland

The pineal gland is made of ependymal cells, photoreceptor-like cells and neurons.<sup>17</sup> The gland is located between the two hemispheres of the telencephalon and the cerebellum. This gland's photoreceptive-like cells are stimulated by light through pinopsin, a pineal-specific photoreceptive molecule, making the pineal a major component of the circadian pacemaking system.<sup>91,117</sup> The pineal's rhythmic synthesis and secretion of melatonin is regulated by neural signals from sympathetic nerves.<sup>92</sup> A second component of the circadian pacemaking system consists of a self-sustained oscillator, which is an area of the hypothalamic region possibly equivalent to the mammalian suprachiasmatic nuclei. The third component, at least in some galliforms and columbiforms, are the retinæ of the eyes.<sup>50,117</sup> These three components work in concert to stabilize and amplify a self-sustaining circadian output. Light is the most powerful stimulus for the circadian rhythm and also can affect the system via the extraretinal/extrapineal photoreceptors located deep in the brain (Fig 19.6).<sup>117</sup> The relative contribution each part plays in keeping the rhythm differs between species and, at times, within the same individual. The predominant factor maintaining rhythm in the house sparrow is the pineal gland, in the pigeon it is both eyes and pineal gland, and in the Japanese quail it is the eyes.

Changes in the pacemaker are partly related to the rhythmic synthesis and release of melatonin. These changes may be important in environmental situations, such as mid-winter and summer in the high arctic where conditions are constant, and also in the ever-changing conditions encountered during migration.<sup>50</sup> In arctic mid-winter and mid-summer birds, and in migratory birds, there is a reduction in melatonin amplitudes. This reduction should result in a reduction in the degree of oscillation of the pacemaking system. A reduction in oscillation reduces the overall output of the pacemaker. This should facilitate adjustments to altered environmental conditions during migration, and in conditions that are more constant, it may enhance entrainability to weak Zeitgeber influences.<sup>51</sup>



**Fig 19.6** | Interactions of the Circadian Pacemaking System

Sometimes in constant conditions, the pacemakers are unable to sustain the persistent rhythm without periodic melatonin input from the eyes or pineal gland, or periodic neural input from the suprachiasmatic nuclei.<sup>117</sup> The most powerful stimuli of synchronization of the circadian rhythm is periodic alteration of light intensity.<sup>2</sup> Light affects melatonin synthesis by entrainment of circadian melatonin rhythms and acute inhibition of melatonin synthesis.<sup>36</sup> Light inhibition of melatonin causes sleep impairment in pigeons.<sup>14</sup>

Retinal photoreceptors appear to mediate light-induced suppression and photic entrainment in pigeons and Japanese quail.<sup>36</sup> Dopamine stimulates retinal melatonin synthesis. Dopamine has shown to have a rhythm of release opposite to melatonin, that is, increased levels in the day and decreased levels at night. Experiments have demonstrated that the interaction of dopamine and melatonin are necessary for maintaining the anti-phase relationship between the two rhythms.<sup>36</sup>

Melatonin also affects regulation of seasonal changes in immune function by enhancing cell-mediated immunity.<sup>11</sup> As discussed in the Song section in this chapter, melatonin also inhibits the neural plasticity of the song control system.<sup>12,13,36</sup> These seasonal regulations and the action of melatonin appear to be modified by the same

central thyroid-dependent mechanism that controls the reproductive state in birds.<sup>11</sup>

Melatonin helps to time migration and the hatching of eggs, but does not fully coordinate reproductive activity with a favorable time of year.<sup>11</sup> In non-tropical birds, photoperiod is the predominant proximate factor. With increasing photoperiod in the spring, secretion of luteinizing hormone releasing hormone (LHRH) increases and results in gonadal maturation.<sup>61</sup> Breeding terminates while days are still long, due to induced photorefractoriness. The gonadal regression during this time is associated with a large decrease in LHRH. This suggests photoperiodic responses involve direct interactions between photoreceptors and LHRH neurons.<sup>31</sup>

Melatonin synthesis also has been demonstrated in Harderian glands, the gastrointestinal tract and retina. The extrapineal melatonin is only rarely released into the circulatory system. Presumably, it exerts its influence locally.<sup>51,65</sup> High concentrations of melatonin are found in enterochromaffin cells of the mucosal epithelium of the gastrointestinal tract.<sup>65</sup> Pinealectomized pigeons were found to have a 24-hour cycle of melatonin secretion in the gastrointestinal tract, with levels increased at night and decreased during the day.<sup>65</sup> Melatonin receptors have been found in a variety of tissues, which suggests

direct actions of melatonin on the function of different organ systems in response to internal and external stimuli.<sup>102</sup>

With the complex responses seen in birds due to duration and intensity of light, it seems paramount that the bird's natural photoperiod be accommodated. This is true for the home environment as well as the hospital. Night treatments should be done quickly, with an attempt not to shine light toward the head, because even a short duration of light exposure in the night can throw the natural circadian rhythm off. In 24-hour clinics, it is important to keep cages covered during the normal night duration.

## THERMOGENESIS

The pineal gland influences thermoregulation. Pinealectomy performed on some species caused increased core body temperature and decreased tolerance to heat at night.<sup>18</sup> This effect returns to normal with the administration of melatonin. Exogenous melatonin in intact house sparrows decreased core body temperature by 4.7°C within 30 minutes.<sup>16</sup> Melatonin may be an effective antipyretic. Melatonin facilitates sleep and acts to synchronize the decrease in body temperature and metabolic rate in order to reduce energy expenditure during inactive periods.<sup>14</sup>

Another area of the brain that is involved in thermogenesis is the preoptic/anterior hypothalamic area (PO/AH) where warm- and cold-responsive neurons are found.<sup>32</sup> A number of neuroactive compounds have demonstrated effects in this area. When acetylcholine, dopamine, serotonin or norepinephrine were injected into the PO/AH of pigeons, the birds demonstrated peripheral vasodilation, inhibition of shivering and decreases in heat production.<sup>58</sup> Prostaglandin E<sub>2</sub> injected into the hypothalamus caused hyperthermia in pigeons and fowl, whereas prostaglandin F<sub>2α</sub> caused hypothermia in fowl and hyperthermia in pigeons.<sup>87</sup> Arginine vasotocin reduces shivering, body temperature and oxygen consumption, whereas angiotensin-II has the opposite effects.<sup>54</sup>

Thyroid hormones help to adjust the body temperature in response to the environment by increasing T<sub>3</sub> levels in cold and decreasing T<sub>3</sub> levels in warm surroundings.<sup>26</sup> This information implies that the hypothalamus is more an integrator of physiological inputs than a direct controller of thermogenesis.

It is clear that, under most situations, when a clinician is faced with a "sick" bird (excluding head trauma), keeping it warm is very important. If prostaglandins are administered to the bird or the bird's photoperiod is rearranged at this time, it would be prudent to monitor for changes in the patient's body temperature.

## Song

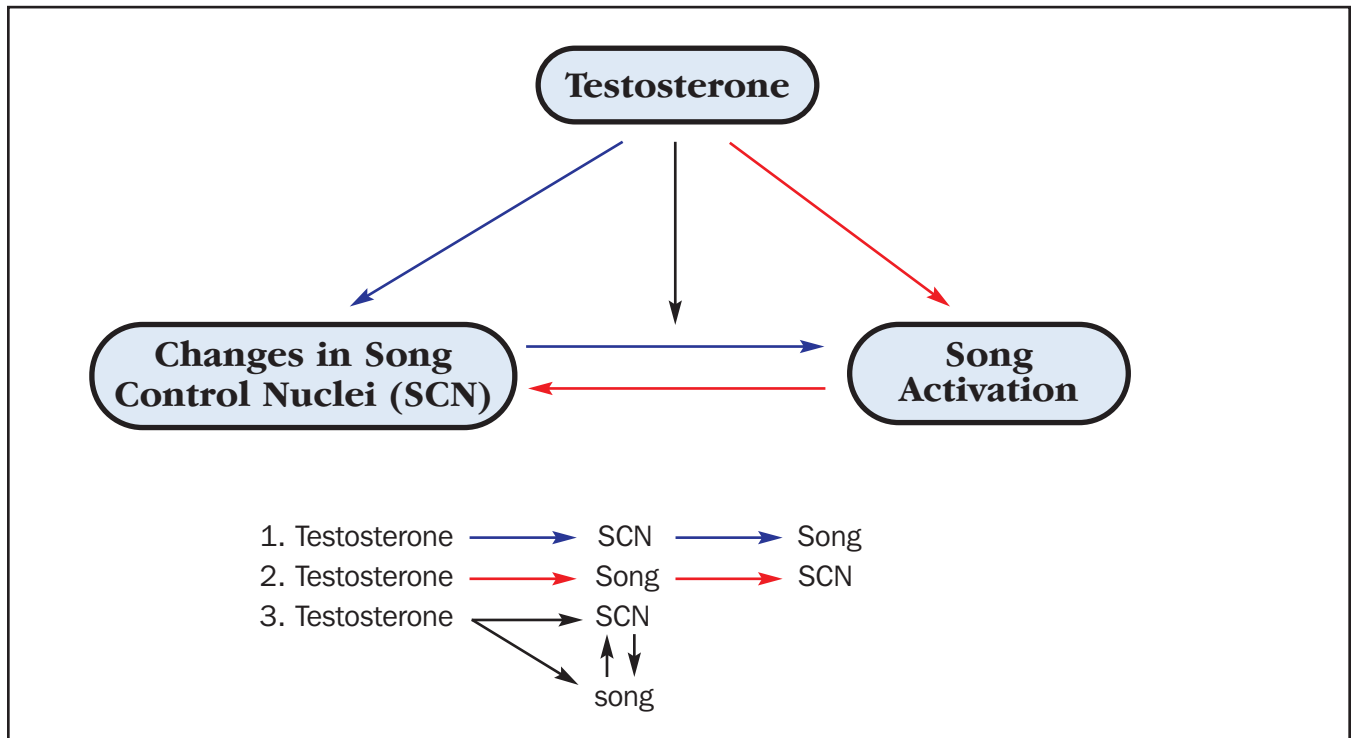
Over the last decade, there has been an increased interest in the effects of hormones on behavior and changes in brain morphology. The complex learned behavior of singing is expressed differently in the different sexes of many species of birds. The current research suggests that steroid hormones can induce a neuroplasticity, which activates this behavior. This seasonal neuroplasticity is more dramatic in birds than in other vertebrates.

In many song birds, most notably the zebra finches (*Taniopygia guttata*) and canaries (*Serinus canaria*), a song control system (SCS) has been identified in the brain. The higher vocal center, a part of this system, appears to be unique to the songbird suborder.<sup>4,21,88</sup> This center is implicated in the learning of new song, as well as the production and perception of previously learned songs.<sup>21,88</sup> Several of the nuclei of the SCS contain high levels of androgen, estrogen, norepinephrine, and acetylcholine muscarinic and dopamine receptors along with acetylcholinesterase.<sup>99</sup> In addition, fibers containing neurotransmitters (catecholamines), or neuropeptides (vasoactive intestinal polypeptide, enkephalin, cholecystokinin, substance P and Metenkephalin) are present.<sup>4,8,9</sup>

Estrogenic metabolites of testosterone increase norepinephrine and dopamine turnover in the SCS, suggesting an interaction between the metabolites of testosterone and these catecholamines.<sup>8,9</sup> Androgen receptors in the SCS appear to be unique to song birds and the Anna's hummingbird (*Calypte anna*), a non-song bird.<sup>38</sup>

In the fall, when singing is not done to attract a mate, daylight is decreasing and sex hormone levels are low. In the song sparrow (*Melospiza melodia*), evidence suggests that the autumnal singing involves estrogen acting locally in the brain. The source of the neuroactive estrogen is unknown, but does not appear to be from testosterone of gonadal origin.<sup>110</sup> The administration of testosterone will increase song rate, whereas castration will reduce, but not always eliminate, male-typical song, depending on the species.<sup>1</sup> Castrated song sparrows in the wild sang at effective rates when territorial challenges occurred.<sup>125</sup> Testosterone influences song quality.<sup>80</sup> Studies indicate that it is the androgenic and estrogenic metabolites of testosterone, through testosterone's aromatization, that are required to completely restore the full rate of singing.<sup>52</sup> It appears that in zebra finches, estrogenic metabolites of testosterone selectively promote courtship song.<sup>121</sup>

Temperate zone wild male songbirds have seasonal peaks of testosterone associated with increasing daylight in the spring. At this time, increases in the volume of song control nuclei occur.<sup>108,109</sup> The song control nuclei



**Fig 19.7** | Song Activation Models.

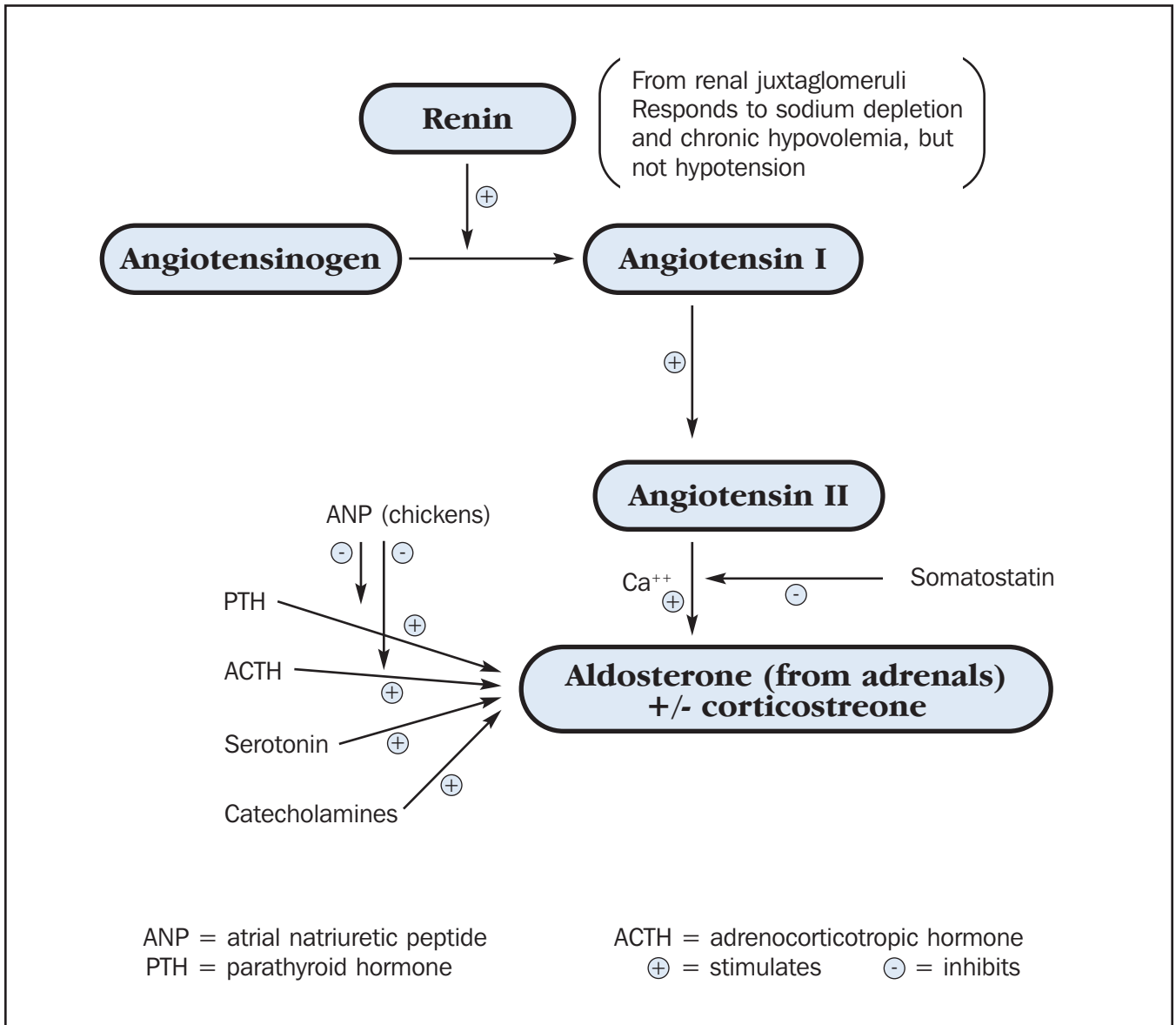
volume increase precedes the growth and development of the reproductive system.<sup>116</sup> Other environmental stimuli clearly play a role. Starlings in captivity, exposed to spring photoperiods, increased the volume of higher vocal center nuclei of the SCS, whereas males kept in outdoor aviaries in the spring had volume increases in the nuclei of most, if not all of the SCS.<sup>10</sup> It is possible that seasonal variation and/or steroid-induced changes in catecholaminergic afferent input into the SCS are important in regulating changes in the vocal learning or production of song, as well as the volume changes in nuclei of the SCS.

A significant amount of research indicates the importance of testosterone on the morphology of the SCS. Testosterone can restore SCS development in castrated males, corresponding to photoperiod changes in both gonad and SCS size.<sup>1,108,109</sup> Testosterone given to females results in male-typical song behavior and increase in the size of their song control systems.<sup>5,115</sup> There also is evidence that the SCS can grow in response to photoperiods independent of testosterone.<sup>6</sup> Recent data indicate that the volume of SCS nuclei correlates with song performance in some cases. It may be that high rates of singing could cause an increase in the SCS.<sup>7</sup> Brain-derived neurotrophic factor that promotes growth of the higher vocal center is released by singing activity. This information helps to

explain the dissociation sometimes observed between steroid-induced and seasonal changes in the song system morphology and vocal behavior (**Fig 19.7**).

Melatonin also may play a role in song system morphology changes. The volume of the song control nuclei was studied in castrated starlings held under different photoperiods to induce reproductive states characteristic of different seasons. Long days are associated with larger volumes of the higher vocal center nuclei than are short days. Melatonin administration attenuated the long day-induced volume increases. The song system also was found to have high densities of melatonin receptors.<sup>12,13</sup> Long durations of melatonin secretion in late fall and winter subdue the effects of testosterone. With long days, melatonin secretion decreases rapidly and testosterone increases. It is apparent that the interaction between many hormones may fine-tune the activity of the SCS.

The SCS and behavior that induces singing are extremely complex. Before administering hormones to induce singing, it is imperative that we learn more about this system. More importantly, good nutrition and a good environment will allow the bird to sing when it is appropriate. A quiet bird out of breeding season may be a happy bird, with no need for male aggressive or territorial singing. Conversely, compulsive singing may be a sign of stress.

**Fig 19.8** | Renin-Angiotensin System.

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