Endocrinology of Obesity

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Obesity is defined as a clinical state of excessive accumulation of body fat. Currently, obesity is considered one of the most important human health concerns, both in the industrialized and developing countries, because it is highly associated with type 2 diabetes mellitus, hypertension, hyperlipidemia, and heart diseases. Although obesity and associated metabolic disorders have been primarily implicated in human health, they are now a growing concern in dogs and cats. In the United States, approximately 35% of adult dogs and cats are overweight or obese. As observed in humans, canine and feline obesity are mainly caused by positive energy balance. Obese dogs and cats have a decreased life span and multiple metabolic disorders. Obesity serves as a direct or indirect cause of various endocrine abnormalities contributing to metabolic disorders. The development of obesity may also be secondary to endocrine disorders in dogs and cats. However, the cause-effect relationship between obesity and endocrine alterations is often unclear. This review focuses on the role of endocrine organs and alterations in response to obesity in humans, dogs, and cats. Although a lack of information on obesity-induced endocrine alterations in dogs and cats exists in the literature, we have attempted to include all relevant published data in these species.

HYPOTHALAMUS AND PITUITARY GLANDS

The hypothalamic-pituitary axis is a neuroendocrine system that regulates various body functions, such as stress responsiveness, the immune response, and energy...
homeostasis. Under control of the hypothalamus, the anterior pituitary produces several hormones that act on target cells of other endocrine organs.

Growth hormone (GH) is secreted from the anterior pituitary, and its secretion is regulated by the hypothalamic hormones growth hormone–releasing hormone (GHRH) and somatostatin. The main function of GH is to enhance growth in young animals. GH plays a role in increasing muscle mass, decreasing body fat, and increasing bone mineralization in adult humans and animals. Numerous studies in humans and rodents indicate that obesity results in a marked decrease in plasma GH concentrations, representing GH deficiency.6–8 It appears that impaired GH secretion is a consequence of obesity because weight loss restores the defect in GH secretion.9,10 It is speculated that this GH deficiency results from diminished pituitary somatotroph responsiveness to GH stimuli, hyposecretion of GHRH, and hypersecretion of somatostatin.10 Hyperinsulinemia and increased plasma free fatty acids associated with obesity also contribute to GH deficiency.8,11 Obesity elevates circulating growth hormone–binding protein (GHBP) concentrations, which may be an adaptive mechanism to increase GH sensitivity in obese subjects.12

Insulin-like growth factor I (IGF-I) is produced by various tissues, mainly the liver, and acts as a physiologic mediator of GH action. Plasma IGF-I concentrations are variable in obese humans but may be expected to be decreased because of GH deficiency.10,13 However, obesity-induced hyperinsulinemia may decrease the expression of IGF-binding protein, thereby increasing free IGF-I concentrations that may exacerbate GH deficiency via the feedback inhibition.7,14 In dogs, obesity induced by prolonged overfeeding resulted in increased plasma IGF-I concentrations, which was positively correlated with hyperinsulinemia.15 In another study of naturally acquired obesity, serum IGF-I concentrations were 80% greater in obese dogs as compared with lean dogs.16 In another study, however, only 20% of obese dogs had elevated serum IGF-I concentrations, demonstrating little correlation with body weight.17

Corticotropin-releasing hormone (CRH) produced by the hypothalamus stimulates the adrenal gland to secrete cortisol via the activation of corticotropin (ACTH) release from the pituitary gland. Obesity is suggested to be the cause of a hyperactive hypothalamic-pituitary-adrenal (HPA) axis. In obese rodents, both plasma corticosterone concentrations and the response of corticosterone and ACTH to exogenous stressors were greatly elevated as compared with lean controls.18 Hyperactivity of the HPA axis was also observed in obese humans.13,19 However, the stimulatory effect of ACTH on cortisol secretion was decreased with obesity; the increase in ACTH was relatively greater than that of cortisol secretion.20 Hyperactivity of the HPA axis may be affected by the location of fat deposition because central obesity induces greater activity of the HPA axis than does peripheral obesity.21 Increased leptin concentrations in obese individuals may also contribute to a hyperactive HPA axis because of leptin’s stimulatory effect on CRH and ACTH production.20 The effect of obesity on the activity of the HPA axis in dogs is not clear. One study reported that only 4 of 31 obese dogs had a hypersecretion of cortisol after intramuscular ACTH injection.17

Thyrotropin-releasing hormone (TRH), secreted from the hypothalamus, stimulates the anterior pituitary gland to release thyrotropin (TSH), which subsequently activates secretion of thyroxine (T4) and triiodothyronine (T3) from the thyroid gland. The hypothalamic-pituitary-thyroid gland (HPT) axis plays an important role in energy homeostasis by modulating basal metabolic rate. Thus, thyroid hormone deficiency decreases basal energy expenditure, which may be a direct cause of obesity.13,22 Hypothyroidism is also a risk factor for canine obesity.5 In
humans, however, obesity induces little change in the basal activity of the HPT axis, although the results are variable.\textsuperscript{13,23,24} Like humans, obese dogs generally have normal thyroid function despite having slightly increased plasma concentrations of total T\textsubscript{4} and T\textsubscript{3}.\textsuperscript{16,25} On the contrary, one study reported that obesity caused increased TSH and decreased free T\textsubscript{4} concentrations in dogs, changes that often indicate subclinical hypothyroidism.\textsuperscript{17} Elevated free serum T\textsubscript{4} concentrations, but normal total T\textsubscript{4} and TSH concentrations have been reported in obese cats.\textsuperscript{26} Thyroid hormone resistance may contribute to altered activity of the HPT axis observed in obese humans and animals.\textsuperscript{26–28} Increased leptin concentrations may also be responsible for modulating the activity of the HPT axis because it is thought to stimulate TRH and, consequently, thyroid hormone production.\textsuperscript{27,29} The cause-effect relationship between obesity and thyroid dysfunction, however, still remains a question in humans and animals.

Prolactin is secreted from the anterior pituitary, with its secretion being controlled by prolactin-releasing hormone (PRH), dopamine, and TRH from the hypothalamus. Prolactin not only has functions pertaining to reproduction and lactation, but also in immune response, osmoregulation, and angiogenesis. In general, basal prolactin secretion is normal in obese humans.\textsuperscript{24} However, one study of obese women reported that serum prolactin concentrations were elevated with increased body mass index and that prolactin secretion rates were specifically associated with visceral fat mass.\textsuperscript{30} Decreased dopaminergic tone, which normally inhibits prolactin secretion, and increased leptin concentrations via its stimulator effects may contribute to increased prolactin concentrations in obese subjects.\textsuperscript{30,31} Moreover, obesity may blunt prolactin responsiveness to various stimuli.\textsuperscript{32} It was reported that obese women had decreased responsiveness to TRH stimulation, demonstrated by decreased prolactin production rates to TRH administration as compared with normal-weight women.\textsuperscript{33} Similar results have been observed in children with mild to moderate obesity.\textsuperscript{34} Increased prolactin concentrations have also been reported in obese dogs and cats.\textsuperscript{17,35}

Obesity influences reproductive functions in both men and women by altering the activity of the hypothalamic-pituitary-gonadal axis.\textsuperscript{36} Adipose tissue also acts as a reservoir of sex hormones. Therefore, obesity may modulate circulating concentrations of sex hormones and the relative ratio of estrogens and androgens.\textsuperscript{37} In obese men, total and free testosterone concentrations decrease as body weight increases.\textsuperscript{36,38} Reduced testosterone concentrations with obesity may be attributed to decreased sex hormone-binding globulin (SHBG) and gonadotropin concentrations.\textsuperscript{36,38} On the contrary, obese women are often reported to show hyperandrogenism as evidenced by increased testosterone and decreased SHBG concentrations.\textsuperscript{39} Similar alterations in circulating testosterone concentrations have been observed in obese male and female dogs.\textsuperscript{16} This dichotomy is difficult to explain, but is partly a result of different HPA axis activity between the sexes.\textsuperscript{19}

Estrogen concentrations tend to be increased in both obese male and female humans probably because expanding adipose tissue elevates the conversion of androgen precursors into estrogen.\textsuperscript{40} Data pertaining to obesity-induced alterations of sex hormones in dogs and cats are scarce. Moreover, the frequent practice of neutering dogs and cats, which is a risk factor for obesity, further complicates the relationship between obesity and sex hormones because it leads to a distinguished state of hormonal homeostasis. For instance, neutering dogs increases luteinizing hormone concentrations because of the absence of negative feedback from androgens and estrogens as well as an alteration of the pituitary response to gonadotropin-releasing hormones.\textsuperscript{41,42} Similar results are expected in neutered cats.\textsuperscript{35}
PANCREATIC HORMONES

Insulin is produced by β cells in the islet of Langerhans of the pancreas and is characterized as an anabolic hormone. Insulin resistance and hyperinsulinemia are well known characteristics of human obesity.40 Similarly, obesity contributes to insulin dysfunction in dogs and cats although the relationship between obesity and insulin function differs between the 2 species.43 In cats, it has been reported that obesity decreases insulin sensitivity by approximately 50%.44 Weight reduction corrects impaired insulin sensitivity and hyperinsulinemia in overweight cats.45,46 It has been calculated that each kilogram of weight gain reduces insulin sensitivity and glucose effectiveness in cats by 30%.46 Obese male cats may be more prone to diabetes than obese females because of a lower innate insulin sensitivity and higher basal insulin concentrations.44 Obese dogs also develop insulin resistance and hyperinsulinemia and are responsive to weight loss, which leads to a recovery of insulin sensitivity and decreased insulin concentrations.15,16,47 Obesity is also associated with pancreatitis in dogs, although no cause and effect has been established, and therefore may lead to an increased risk for developing type I diabetes.48

High fat-induced obesity in dogs decreases insulin accessibility to skeletal muscle, resulting in decreased insulin sensitivity.49 Visceral obesity results in greater insulin resistance and hyperinsulinemia than peripheral obesity in human beings,47 but it is not known if the same holds true for dogs and cats. Increased concentrations of free fatty acids and inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), produced by visceral fat are thought to be possible reasons for this observation.15,47 Increased leptin concentrations may also contribute to insulin resistance by impairing insulin function in various insulin-dependent tissues.50 Insulin resistance with diet-induced obesity also appears to be more pronounced in adult or mature dogs than in young dogs.51

Glucagon is produced by pancreatic α cells and is known as an antagonistic hormone of insulin. Therefore, hyperinsulinemia secondary to obesity may be expected to decrease glucagon production. However, there is evidence that glucagon resistance exists in humans and rodents, resulting in increased circulating glucagon concentrations.52–54 It appears that glucagon resistance derived from obesity is caused by insulin resistance of pancreatic α cells.55

Amylin is also produced by pancreatic β cells and is secreted with insulin. Amylin functions with insulin synergistically but has inhibitory effects on glucagon secretion. Thus, amylin secretion following a meal results in a metabolic switch from endogenous glucose production to dietary glucose use.55 It is reported that plasma amylin concentrations increase in obese humans and decrease after weight loss.56,57 Increased insulin secretion as a result of insulin resistance may be a cause of increased amylin production.57 Overexpression of amylin results in pancreatic islet amyloidosis and impairs β-cell function, which may in turn exacerbate insulin dysfunction.55,57 Given the species similarities as it pertains to insulin resistance, obesity is also expected to elevate amylin concentrations in obese dogs and cats.58,59

Pancreatic polypeptide (PP) is secreted primarily by PP cells in the pancreatic islets of Langerhans and functions by suppressing gastric emptying, pancreatic enzyme secretion, and appetite.60 Decreased PP concentrations have been observed in human obesity, but are normalized after weight loss, indicating that obesity is a causal factor in its reduction.61–63 In humans, PP concentrations were greater in obese subjects with glucose intolerance as compared with obese subjects with normal glucose tolerance, indicating that insulin sensitivity may be a confounding factor between obesity and plasma PP concentrations.54 It was also reported that PP
secretion, either in response to hypoglycemia or after a meal, was impaired in obese humans. However, the underlying mechanisms for low PP concentrations as a consequence of obesity have not been fully elucidated.

ADIPOSE TISSUE

Adipose tissue is composed of numerous cell types, including adipocytes, fibroblasts, macrophages, and endothelial cells. The primary role of adipose tissue is to store energy in the form of lipids. However, adipose tissue is also now appreciated as an active endocrine organ that synthesizes and releases metabolically active substances, termed adipokines, which act systemically or locally to influence various metabolic reactions. Several adipokines such as leptin, adiponectin, and resistin have been identified in humans and animals. Increased fat mass has been implicated in the dysregulation of adipokine production and contributes to various obesity-related metabolic abnormalities.

Leptin has been the most widely studied among adipokines in humans and animals. Leptin is known as an antiobesity hormone. In general, leptin functions to decrease food intake, increase energy expenditure, and modulate glucose and fat metabolism through central and peripheral systems. As observed in humans and rodents, plasma leptin concentrations in dogs and cats increase with increasing body fat mass and adipocyte size, and subsequent weight loss leads to decreased leptin concentrations. Therefore, plasma leptin concentration is considered a biomarker for the degree of obesity in dogs and cats, regardless of breed, sex, and age. In an early experiment, exogenous leptin administration was shown to reverse obesity in leptin-deficient mice. However, consequent experiments in humans and animals have consistently reported elevated leptin concentrations in obese subjects, emphasizing the leptin resistance that occurs with obesity.

Leptin is usually thought of as a long-term regulator of body weight. However, it was reported that postprandial plasma leptin concentrations tend to decrease in lean but not obese people, indicating decreased leptin action in the short term as well. Defective leptin receptors or impaired signaling in target tissues may be a cause of decreased leptin sensitivity and leptin resistance. In a canine study, increased serum leptin concentrations but defective leptin transport through the blood-brain barrier was observed as dogs became obese. Plasma leptin is present in a free or a protein-bound form. It has been suggested that an imbalance between free and bound forms of leptin may be associated with increased leptin resistance because free leptin concentrations increase in obese people, whereas most leptin is bound to protein in lean people.

Adiponectin is also produced and secreted exclusively from adipose tissue in humans, dogs, and cats. Adiponectin has been considered a beneficial adipokine because it improves insulin sensitivity by enhancing fat and carbohydrate oxidation in peripheral tissues, suppressing hepatic gluconeogenesis, and inhibiting inflammatory responses. Although it is the most abundant adipokine produced by adipose tissue, obesity results in decreased adiponectin gene expression and plasma adiponectin concentrations in humans and rodents. Decreased plasma adiponectin concentrations have been observed in dogs with experimentally induced and clinical obesity. Likewise, obese cats have significantly lower plasma adiponectin concentrations than normal cats. Therefore, it appears that plasma adiponectin, in addition to leptin, can be a biomarker for body condition status in dogs and cats.
It is suggested that defective adiponectin secretion in obesity is caused by increased feedback inhibition from inflammatory cytokines such as TNF-\(\alpha\) and IL-6, which are escalated with body fat mass.\(^8^4\) Moreover, obesity is likely to decrease the expression of adiponectin receptors in both muscle and liver, leading to adiponectin resistance that is highly related to insulin resistance.\(^8^5\) Alteration in the circulating forms of adiponectin (low molecular weight [LMW] versus high molecular weight [HMW]) may occur during the development of obesity. In morbidly obese humans, the relative ratio of HMW to total adiponectin decreased with obesity but increased after gastric-bypass surgery.\(^8^6\) Normal levels of HMW adiponectin but decreased levels of LMW adiponectin was also reported in obese humans.\(^8^7\) The differing molecular weight forms of adiponectin have not been examined in dogs or cats.

Resistin is another adipokine and is induced by adipogenesis, although circulating mononuclear cells (eg, macrophages) are probably the main source of resistin in humans.\(^8^8,8^9\) Resistin has gained great attention because of its antagonistic effect on insulin function in mice.\(^9^0\) Moreover, there is evidence that the level of plasma resistin increases in obese mice and humans.\(^9^0,9^1\) In a study with morbidly obese humans, resistin mRNA expression in adipose tissue was increased in obese subjects but was undetectable in lean subjects.\(^8^9\) However, the relationship between obesity and resistin is still inconclusive in humans. Resistin expression has not been studied in dogs and cats.\(^6^6\)

Adipose tissues also produce a variety of proinflammatory cytokines such as TNF-\(\alpha\) and IL-6, which were originally studied for their role in various immune cells. The primary role of TNF-\(\alpha\) and IL-6 is to activate the immune system in response to infection or cancer. However, overproduction of these cytokines has been considered a risk factor in various human diseases. Increased infiltration and accumulation of macrophages in adipose has been observed in obese subjects, which explains the increased expression of TNF-\(\alpha\) and IL-6 during the expansion of adipose tissues.\(^9^2\) Regardless of what cell type is secreting these substances, adipose is appreciated as an active immunologic tissue.\(^9^3\) It is well known that obesity increases the production and circulating concentrations of both TNF-\(\alpha\) and IL-6 and that weight reduction neutralizes them. Therefore, obesity represents a chronic low-grade inflammatory condition.\(^8^2,9^4\)

In dogs, markedly increased plasma TNF-\(\alpha\) concentrations were observed after 30 weeks of overfeeding as compared with a healthy weight at baseline.\(^1^5\) The authors observed a 27-fold increase in plasma TNF-\(\alpha\) during very rapid weight gain in the first 20 weeks of overfeeding. From weeks 20 to 30, a time at which an obese condition was maintained, plasma TNF-\(\alpha\) concentrations tended to decrease but were still 10 times greater than baseline. The reason for decreased plasma TNF-\(\alpha\) during the maintenance of obesity is still unclear, but may be attributed to increased activity of peroxisome proliferator activated receptor \(\gamma\) (PPAR\(\gamma\)) that has inhibitory effects on TNF-\(\alpha\) expression.\(^1^5\) As observed in dogs, TNF-\(\alpha\) expression in adipose tissue and skeletal muscle was much greater in obese than in lean cats.\(^9^5,9^6\) Published data in humans and animals consistently indicate that overexpression of TNF-\(\alpha\) and IL-6 complicates obesity-associated metabolic syndromes, such as insulin resistance, cardiovascular diseases, and osteoarthritis, via impaired insulin signaling, dyslipidemia, and stimulation of hepatic C-reactive protein.\(^9^3,9^4,9^7,9^8\)

**GASTROINTESTINAL HORMONES**

Several hormones are synthesized and released by the gastrointestinal tract (GIT). Although the research focus of these hormones has often been limited to the GIT itself, GIT hormones are now appreciated as active regulators of appetite, satiety, and body
energy balance. Therefore, GIT hormones are assumed to be closely linked with the development of obesity and have been implicated in its prevention.

Ghrelin is synthesized primarily by the X/A-like cells in the oxyntic glands of the gastric fundus and is known to stimulate GH release. Plasma ghrelin is present in the circulation in 2 major forms, depending on the acylation of its serine residue by n-octanoic acid. Although deacylated ghrelin is predominant in circulation, acylated ghrelin is known as an active form. Ghrelin has been recognized as the only orexigenic GIT hormone, with concentrations peaking before a meal and decreasing postprandially. Ghrelin exerts its effects through a GH secretagogue receptor that is ubiquitously present in the body, indicating that it is associated with a variety of bodily functions. Although ghrelin may have an adipogenic property, plasma ghrelin concentrations decrease with obesity in humans and dogs. Weight reduction induced by energy restriction in obese humans and dogs has been reported to normalize plasma ghrelin concentrations.

Decreased ghrelin concentrations may be caused by obesity-induced hyperleptinemia and hyperinsulinemia because they are inversely associated with plasma insulin and leptin concentrations in humans and dogs. It is speculated that this suppression of ghrelin expression is an adaptive mechanism to the surplus of energy stores with obesity. However, a reduced ability to decrease postprandial ghrelin concentrations in obese humans has been observed, which may explain hyperphagia even in a state of obesity. Because exogenous ghrelin administration increased food intake of obese humans in a dose-dependent manner, its inhibition by leptin and insulin may be a more likely reason for continued hyperphagia than ghrelin resistance.

Cholecystokinin (CCK) is secreted by I cells in the proximal small intestine and is known to promote nutrient digestion and to induce a negative feedback inhibition on appetite through the hypothalamus. The major forms of plasma CCK include CCK8, CCK22, CCK33, and CCK58, which are denoted by different numbers of amino acids. The data for CCK as it pertains to obesity is highly variable and contradictory. It was reported that obese women had greater fasting CCK concentrations than lean women, suggesting CCK’s defensive action against overeating. In contrast, one study showed markedly lower fasting and postprandial CCK concentrations in obese women as compared with lean women, indicating it as a reason for increased food intake with obesity. There is also evidence that basal CCK concentrations are similar among nonobese, obese premenopausal, and postmenopausal women. To our knowledge, no data are available on obese dogs and cats. Therefore, the effects of obesity on CCK regulation remain a question in humans and companion animals.

Glucagon-like peptide-1 (GLP-1) is produced by endocrine L cells in the distal small intestine and the large intestine. The processing of preproglucagon by prohormone convertase 1 and 2 produces GLP-1, GLP-2, and oxyntomodulin, depending on the cleavage site. GLP-1 is subsequently cleaved to form the biologically active peptides of GLP-1 (7–37) or GLP-1 (7–36) amide. With the presence of nutrients in the small intestinal lumen, GLP-1 suppresses gastropancreatic secretion and gastric emptying under hypothalamic control and subsequently decreases food intake. GLP-1 is also an “incretin” factor, stimulating insulin and inhibiting glucagon secretion after a meal. A reduced postprandial GLP-1 response has been reported in obese as compared with lean humans. Increased plasma glucose and free fatty acid concentrations, often a result of obesity, have been considered factors for blunted GLP-1 response with weight gain. However, postprandial GLP-1, glucose, and free fatty acid concentrations have not been strongly correlated in obese
humans. In contrast to humans, one study reported a tendency for greater GLP-1 concentrations in obese than lean dogs. However, no further data have been published to support this initial observation in dogs.

Peptide YY (PYY) is coproduced with GLP-1 by endocrine L cells in the distal small intestine and the large intestine. Two biologically active forms of PYY, PYY-1 (1–36) and PYY-2 (3–36), have been identified; PYY-2 is a predominant form in the circulation. PYY and GLP-1 have very similar biologic functions, suggesting that these 2 hormones complement each other. As observed in GLP-1 response, fasting and postprandial plasma PYY-2 concentrations have been reported to be lower in obese than in lean humans. Postprandial plasma PYY-2 concentrations, which are typically increased in normal-weight subjects after a meal, were blunted in obese subjects. This observation demonstrates that increased food intake with obesity may be partly a result of decreased plasma PYY concentrations. However, obese humans showed no PYY resistance, as exogenous PYY infusion resulted in a similar reduction in caloric intake.

### Table 1

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<tr>
<th>Hormone</th>
<th>Humans</th>
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<tr>
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<td>Peptide YY</td>
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**Abbreviations:** ACTH, corticotropin; CRH, corticotropin-releasing hormone; IGF-I, insulin-like growth factor-I; IL-6, interleukin-6; ND, no data available; T₃, triiodothyronine; T₄, thyroxine; TNF-α, tumor necrosis factor α; TRH, thyrotropin-releasing hormone; TSH, thyrotropin; ↑, increase; ↓, decrease.
between obese and lean humans.\textsuperscript{114} To our knowledge, the effect of obesity on PYY has not been examined in dogs and cats.

**SUMMARY**

Obesity is believed to induce various endocrine alterations and is characterized by blunted responsiveness to stimuli and hormonal resistance. Many of these alterations not only occur during the development of obesity but also modify metabolic systems that promote further weight gain and/or disease. Obesity-associated endocrine alterations are presented in \textit{Table 1}, although the results are still inconclusive in many areas. Most abnormal hormone concentrations are corrected by weight reduction, which implicates obesity as a direct cause of the endocrine alterations. Several physiologic factors, including age, sex, puberty, and health status of obese subjects complicate the relationship between obesity and endocrine alterations. Significant hormone-hormone interactions, which were highlighted throughout the review, further complicate our understanding of their role in normal and obese states. It is clear, however, that a considerable amount of crosstalk occurs within and between tissues. Thus, research using whole animals must be sustained to fully understand these complicated systems. There has been a lack of published data pertaining to hormonal functions and the effects of obesity in dogs and cats. It may be conceivable that obesity-related hormonal alterations observed in humans are comparable to those of dogs and cats, but future research is required to verify this assumption.

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