Osteopathic Family Physician (2010) 2, 180-186

ELSEVIER

acofp Osteopathic Family Physician

The role of socioeconomic stress in the risk for obesity and diabetes: potential new targets of treatment

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KEYWORDS:
Type 2 diabetes mellitus;
Stress

Our health can be negatively affected by chronic stress. Stress can be normal variable hassles of daily life, life events, or sleep disruption, or it can be the more chronic social stresses related to personal role in community, economic status, or status incongruity. Socioeconomic stress is often overlooked as being a significant contributor to the increased prevalence of many chronic diseases like obesity, diabetes mellitus, cardiovascular disease, and cancer; however the evidence is now compelling. Although correlations between socioeconomic stress and chronic disease have been made, the physiologic mechanisms by which socioeconomic stress results in increased risk remain poorly understood and are only now being explored. For example, chronic stress can lead to a chronic increase in cortisol secretion, leading to accelerated lipolysis, truncal obesity, and insulin resistance, which are risk factors for the development of type 2 diabetes. We will review our current understanding of how socioeconomic stress contributes to the development of obesity, insulin resistance, and type 2 diabetes, and discuss newer targets for therapy based on these observations.

Humans through evolutionary design have been programmed to store energy in times of adequate food availability to protect themselves from starvation when food is less readily available. However, today in times of relative abundance of food, there is still a tendency to store excess calories, which has resulted in an increase in the prevalence of obesity and type 2 diabetes mellitus (T2DM). Although the existence of starvation has virtually been eliminated in the United States, less severe forms of hunger and food insecurity (fear of hunger) are still found within the United States, and this food insecurity has been linked to increased rates of obesity, T2DM, and premature cardiovascular disease.

Type 2 diabetes mellitus

Type 2 diabetes mellitus is a chronic disease associated with obesity, insulin resistance, compensatory hyperinsulinemia, eventual beta cell failure, and consequent hyperglycemia. There is a general consensus that acquisition of visceral obesity (intraabdominal) plays a pivotal role in the development of insulin resistance, T2DM, and atherosclerosis. Visceral adipocytes, which function to store dietary fat, once saturated, begin to produce excess amounts of various biologically active cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which directly induce insulin resistance.[1] In insulin target tissues such as liver and muscle, TNF-α induces insulin resistance by decreasing serine phosphorylation of the insulin receptor kinase, whereas IL-6 induces insulin resistance by inhibiting glucose transport 4 (GLUT4) synthesis. In addition, saturated visceral adipocytes release excess free fatty acids (FFAs)/nonesterifed fatty acids. Excessive FFAs in the circulation also contribute directly to the development of in-

Frank Schwartz has a financial affiliation with studies and patenting of Phenylmethimazole (C10).

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1877-573X/$ -see front matter © 2010 Published by Elsevier Inc.
doi:10.1016/j.osfp.2010.08.001

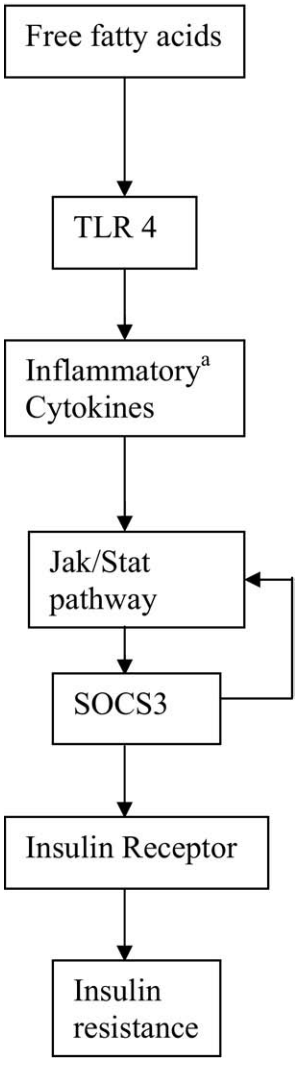

Figure 1 Hypothesized pathway by which insulin resistance occurs in type 2 diabetes. *a*, TNF-α, IL-6.

sulin resistance through ectopic deposition in insulin-sensitive tissues (liver and muscle), where they also release these same inflammatory cytokines.[1-6] We have demonstrated that free fatty acids such as palmitate also directly activate the innate immune system through pathologic expression of toll-like receptor (TLR) expression and signaling in nonimmune cells such as 3T3L1 adipocytes. TLRs are a family of cell surface receptors normally found on immune cells that recognize microbial or cellular products and initiate our innate immune response to environmental pathogens.[1] TLR3, for example, recognizes double-stranded ribonucleic acid (dsRNA) from viral-damaged cells, then activates MHC genes important for immune cell interactions and an antiviral gene response.[2] Harii et al. were the first to describe functional TLR3 in nonimmune cells (thyrocytes) and show that TLR3 is overexpressed in thyrocytes from patients with Hashimoto's thyroiditis.[3] TLR3 has also been demonstrated in beta cells from individuals with new-onset type 1 diabetes mellitus.[4] TLR4 normally function recognize bacterial lipopolysaccharides in immune cells and, like TLR3, activate genes important for immune cell interactions and an antibacterial response.[5] We have shown that palmitate similar to lipopolysaccharides directly activates TLR4 signaling in nonimmune cells such as 3T3L1 adipocytes, and that this activation of TLR4 increases expression of IL-6 and TNF-α, which are the same cytokines that induce insulin resistance. This suggests that the innate immune system via pathologic activation of TLR4 in nonimmune cells may also play a role in the pathogenesis of T2DM (Fig. 1).

Chronic stress

The disproportionately higher prevalence rates of depression, obesity, T2DM, and cardiovascular disease observed within socioeconomically at-risk populations, where food sources are often inadequate, seemed initially to conflict with this hypothesis.[7-9] However, socioeconomic stress itself is now thought to be a major contributor to the increased prevalence of many chronic diseases. Chronic stress can have a cumulative negative impact on health over time. Stress has been shown to upregulate the sympathetic adrenal medullary axis to increase the secretion of epinephrine and norepinephrine, and the hypothalamic pituitary adrenal cortical axis to release cortisol (Fig. 2). Stress-induced increases in epinephrine, norepinephrine, and cortisol secretion result in increases in heart rate and blood pressure, and changes in carbohydrate and fat metabolism, triggering increased glucose mobilization that contributes directly to the development of insulin resistance. In response to these hormones, visceral adipocytes produce the same inflammatory cytokines, TNF-α and IL-6, which contribute to the induction of insulin resistance. Thus, stress can contribute to the development of diabetes acutely via mobilization of glucose and FFAs and chronically by stimulating the acquisition of visceral obesity.

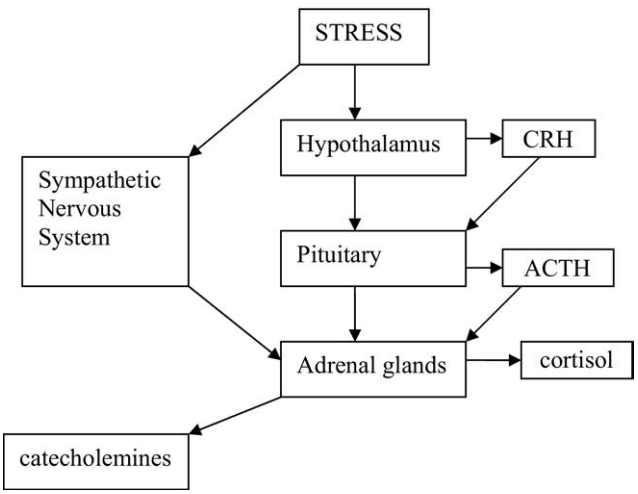

Figure 2 Pathways and hormones involved with the stress response. When chronic, they can lead to poorer lifestyle choices and weight gain.

Socioeconomic stress

Socioeconomic stress is the chronic strain of attempting to meet basic survival needs without enough resources to do so or living up to the expectations set by others in the same social arena. Socioeconomic status is defined primarily by education and income levels. People in lower socioeconomic status brackets have higher prevalence rates of most chronic diseases, including obesity, diabetes, cardiovascular disease, and cancer, as well as higher morbidity and mortality rates from these diseases. In addition, the psychosocial stress of poverty itself may contribute directly to the increased risk for chronic illness.

Studies correlating socioeconomic stress with urine metabolites of epinephrine and norepinephrine, such as vanillylmandelic acid or serum cortisol levels, have shown the highest stress hormone levels in lowest income quartiles. Lower socioeconomic status is also associated with increased central adiposity[10,11] and decreased leptin, which is a major satiety hormone involved in decreasing food intake control.[12] Stress eating is a common observation and stress hormones can result in decreases in serum levels of leptin, which is a major satiety signal. This might explain how chronic emotional stress leads to overeating and weight gain.[12] Food insecurity and fear of hunger have also been linked to increased rates of obesity, diabetes, and poorer glucose control.

Chronic stress promotes adverse changes in mood and cognition, all of which can affect food intake, both total calories and food choices. During times of stress, it is part of typical human behavior to choose foods that are higher in calories and carbohydrates. These types of food also tend to be cheaper and more convenient, which makes them more appealing when on a budget with respect to time or money. The combination of stress and poor eating contribute to the development of visceral obesity and the risk for development of T2DM. More research needs to be done to determine the precise mechanisms by which psychosocial stress associated with poverty and economic disparity contribute to the pathogenesis of chronic diseases like diabetes.

Food insecurity and fear of hunger have also been linked to increased rates of obesity, diabetes, and poorer glucose control. In at-risk communities, individuals with T2DM were also more likely to live in food-insecure households compared with those without T2DM, and persons with diabetes who exhibited glycosylated hemoglobin levels higher than 7% were more likely to come from food-insecure households compared with diabetics with levels lower than 7%. These observations taken together suggest that poverty, food insecurity, and economic disparity are strongly linked to the risk for obesity and T2DM. A study conducted in monkeys showed that in groups of monkeys that were insecure in obtaining food developed obesity and hyperinsulinemia[13] compared with control animals. Food insecurity is a form of socioeconomic stress, and although monkeys do not directly experience socioeconomic stress, this study demonstrates that the stress of meeting basic needs can lead to obesity and hyperinsulinemia. This study in primates demonstrated that food insecurity leads to changes in eating behavior, leading to changes in carbohydrate and fat metabolism, which results in increased glucose mobilization and insulin resistance.

The obvious solution to reduce the negative impact of poverty and socioeconomic stress on the prevalence of obesity, T2DM, and other chronic diseases would be to eliminate it. However, this is a very complex problem with multiple political, cultural, and economic barriers. Most interventions designed for stress management, including support groups, individual psychological therapy or counseling, stress management, or relaxation techniques, are limited with respect to access in these at-risk populations. Several new therapeutic targets designed to combat obesity and insulin resistance are currently in development including 11β-hydroxysteroid dehydrogenase (11β-HSD) inhibitors, leptin, ghrelin, insulin-like growth factor-1 (IGF-1), and specific TLR inhibitors. The physiology of each compound and their potential role in the treatment of obesity and T2DM are discussed here.

New treatment targets

11β-HSD inhibitors

Cortisol is one of the stress hormones previously described that is chronically elevated in at-risk populations and individuals in the lowest socioeconomic quartile. Cortisol is a major regulator of hepatic gluconeogenesis and adipocyte lipolysis. Its secretion is elevated during periods of stress, acute illness, or trauma, resulting in excessive glucose production, increased lipolysis, increased inflammatory cytokine release (TNF-α and IL-6), and insulin resistance. Cortisol is the hormone principally responsible for the stress-induced hyperglycemia observed in these conditions. Cushing's syndrome is a disease characterized by increased cortisol secretion, and it also results in excessive glucose production, increased lipolysis, central adiposity, insulin resistance, and glucose intolerance or overt T2DM. Cortisol is mildly elevated in obese patients, but there is also an increase in peripheral metabolism that involves increased conversion of cortisol to reduced derivatives as well as decreased hepatic conversion of cortisone to cortisol.[14-16] The enzyme 11β-HSD is in the glucocorticoid hormone synthesis pathway. Both 11β-HSD type 1 and type 2 are located in the liver, whereas only 11β-HSD type 1 is expressed primarily in adipocytes. In the liver, 11β-HSD type 2 functions as a reductase enzyme and metabolizes cortisol to cortisone, which is inactive glucocorticoid, whereas 11β-HSD type 1 metabolizes cortisone back to cortisol. Thus, these enzymes work together to regulate the amount of cortisol within the liver.

Expressed primarily in adipocytes, 11β-HSD type 1 metabolizes inactive cortisone back into the active cortisol molecule. This 11β-HSD type 1 enzyme activity can be induced by glucocorticoids or proinflammatory cytokines[17] in adipocytes, and it has been hypothesized that the enhanced conversion of cortisone to cortisol in adipose tissue is important in the induction of visceral adipogenesis characteristic of central obesity.[14,17] It has also been hypothesized that decreased hepatic cortisol 11β-HSD type 1 expression is a compensatory mechanism to decrease fasting hyperglycemia and improve insulin sensitivity in individuals with visceral obesity and T2DM.[17] Wake et al.[18] state that increased 11β-HSD activity causes an increase in obesity and hyperinsulinemia. Stewart et al. have hypothesized that an imbalance of the 11β-HSD type 1 and type 2 enzyme activity leads to "hepatic and adipocytes glucocorticoid excess," which contributes to excess gluconeogenesis and insulin resistance associated with visceral obesity and T2DM. In either capacity, 11β-HSD has a role in T2DM and visceral obesity.

Levels of 11β-HSD1 are increased in adipose tissue and decreased in liver in obese patients. In contrast, lean patients with T2DM have normal adipose 11β-HSD1 and less marked down regulation of hepatic conversion of cortisone to cortisol. Theoretically, selective inhibition of 11β-HSD1 and/or the upregulation of 11β-HSD2 could prove beneficial in the treatment of T2DM because increased endogenous cortisol may be a factor in the development of insulin resistance.

Other compounds have also been shown to affect 11β-HSD activity as well. For example, both caffeinated and decaffeinated coffee extracts inhibit 11β-HSD and inhibit reduction of cortisol to cortisone.[19] Licorice derivatives glycyrrhizic acid and glycyrrhetinic acid are also potent inhibitors of 11β-HSD, and their proposed mechanism of action is inhibition of the mRNA coding for 11β-HSD, which has been shown to increase the activity of glucocorticoids in rats (Fig. 3).[20] Carbenoxolone, a drug derived from licorice, is a nonselective inhibitor of 11β-HSD1.[21,22] One study demonstrated that carbenoxolone decreases the generation of bioactive cortisol[22]; however, a subsequent study demonstrated that carbenoxolone did not significantly alter glucose and insulin concentrations.[21] However, by also inhibiting renal 11β-HSD2, carbenoxolone has unacceptable long-term side effects including raising blood pressure. Clinical effectiveness of this compound will require selective 11β-HSD1 inhibitors that lower intra-adipose cortisol levels and enhance peripheral glucose uptake.

Leptin

Leptin is an adipokine produced by visceral adipocytes previously mentioned and has been shown to be very important in regulating food intake in the hypothalamus as well as energy balance peripherally[23] via the HPA axis in the adrenal gland.[24] Specific leptin receptors have been demonstrated in various regions of the brain and peripheral

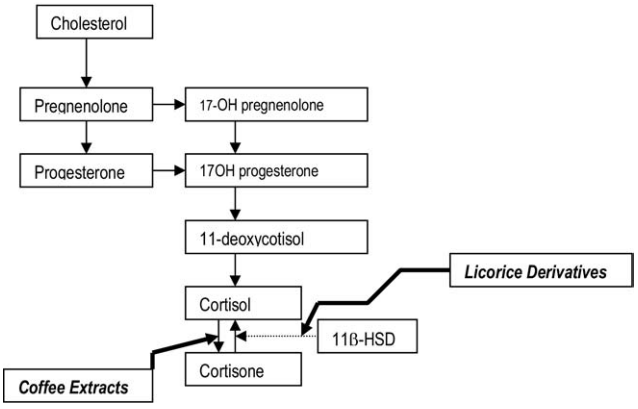

Figure 3 Metabolism of cortisol. Licorice derivatives like glycyrrhizic acid and glycyrrhetinic acid or the drug carbenoxolone inhibit 11β-HSD1 specifically. Coffee extracts have also been shown to inhibit the conversion of cortisol to cortisone via 11β-HSD.

tissues such as the adrenal gland. However, use of leptin to suppress appetite was shown to be ineffective in patients with visceral obesity because they exhibited elevated leptin levels secondary to down-regulation of leptin receptors in the hypothalamus. The cellular mechanism of leptin receptor resistance in the hypothalamus is similar to insulin resistance and is mediated through cytokine-induced factors that directly affect both insulin and leptin signaling at the receptor level including the suppressor of cytokine signaling 3 (SOCS3) in the Janus kinase/signal transducer and activation transcription protein (Jak/STAT) pathway.[2] Activation of the Jak/STAT pathway leads to an inhibitory feedback loop of leptin signaling.[25] These observations imply that the same inflammatory cytokines, TNF-α and interferon-β, which induce insulin resistance, may be mediating the leptin resistance. Leptin resistance is also a common finding in T2DM.[26,27] The presence of leptin resistance has precluded its use in most forms of obesity and T2DM.[28] However, inhibitors of pathologic TLR expression in adipocytes may also decrease both insulin and leptin resistance (see section on TLRs).

Ghrelin

Ghrelin is a peptide hormone that is orexigenic, meaning that it promotes appetite. It is secreted primarily in the fundus of the stomach and in the small intestine, with smaller concentrations in the lungs, pancreatic islets, adrenal glands, gonads, thyroid, placenta, kidney, and brain.[28] Similar to leptin, ghrelin's opposite effects on appetite and effects on energy metabolism have made it a substance of great research interest. Secretion of ghrelin occurs in a pulsatile manner, where it is highest before eating and then decreases with food intake. It is also involved in regulation of energy balance and communicates the status of energy stores in the body to the brain.[30,31] The effects of ghrelin on food intake and energy storage have been linked to obesity.

Ghrelin causes people to consume and store more calories than they need, and these calories are stored as fat.[31] Ghrelin levels are lower in persons with obesity and are increased in lean individuals or in persons who lose weight.[32,33] Central injections of ghrelin lead to an increase in glucose and fat storing enzymes, whereas peripheral injection of ghrelin causes weight gain without increase in food intake.[34] Increased ghrelin levels in response to diet-induced weight loss promote increased food intake and make weight loss more difficult.[35] Ghrelin increases gastric emptying leading to an increase in food intake, so it is possible that a ghrelin antagonist could be used to slow down gastric emptying,[35] cause earlier satiety, and reduce food consumption. Peptide YY, which is found in L cells of the gastrointestinal tract—especially in the ileum and colon—is stimulated by eating, inhibits gastric motility, and decreases ghrelin secretion. Together, ghrelin and peptide YY also act on the arcuate nucleus to regulate appetite.[34]

The relationship between insulin, glucose, ghrelin, and T2DM is unclear. Both oral and intravenous glucose decrease ghrelin levels.[29] Studies have shown that low circulating ghrelin levels are proportional to insulin sensitivity[30]; that is, insulin and ghrelin levels are inversely related in T2DM.[29,31] The effect of the oral antidiabetic compound metformin, which exhibits modest weight-reducing activity clinically, has been shown to suppress postprandial plasma on ghrelin concentrations longer than diet alone in individuals with T2DM.[35] The development of a specific ghrelin antagonist might be beneficial to suppress appetite in obesity and T2DM treatment.

IGF-1

IGF-1 is a peptide hormone produced primarily by the liver that has properties similar to insulin to decrease glucose output by the liver. Its synthesis and secretion is regulated primarily by growth hormone, and it is a potent stimulator of cell growth and multiplication, and a potent inhibitor of programmed cell death. IGF-1 is also an endogenous insulin sensitizer, and IGF-1 administration normalizes insulin resistance in obese individuals and is effective at reducing glucose and hemoglobin A1c levels, as well as insulin requirements in both type 1 diabetes and T2DM. However, in trials where it was administered to patients with diabetes and preexisting retinopathy, it caused progression of the retinopathy and the studies were suspended.[36]

TLR inhibitors

TLRs are pattern recognition receptors that recognize environmental elements of bacteria and viruses and appear to be important components of the innate immune system. Inappropriate TLR expression in nonimmune cells has now been associated with disease expression.[1-6,37-44] Pathologic expression of TLR3 in nonimmune activated genes that increase inflammatory cytokines and costimulatory molecules which are important in the pathogenesis of many autoimmune diseases including Hashimoto's thyroiditis and type1 diabetes. They are also involved in the growth and migration of certain cancers such as papillary thyroid cancer; malignant melanoma; and carcinoma of the pancreas, colon, breast, and prostate. As mentioned previously, FFAs such as palmitate directly activate pathologic expression of TLR4 expression in 3T3L1 adipocytes and that TLR4 activation increases the expression of IL-6 and TNF-α. These are the same cytokines that induce insulin resistance and contribute to the development of T2DM. The development of a compound that would selectively inhibit pathologic expression of TLR signaling without affecting normal TLR function in immune cells would be an important new therapy. Phenylmethimazole (C10) is a derivative of methimazole, a drug used to treat autoimmune Graves' disease and suppress thyrotrophin receptor antibody formation. Leonard Kohn and colleagues developed C10, which has been shown to inhibit pathologic TLR expression and signaling in a variety of disease models including diabetes and cancer.

TLR4 signaling has been hypothesized to regulate the inflammatory markers through the Jak/STAT pathway where SOCS3 is upregulated. Secretion of inflammatory markers decreases insulin sensitivity in fat cells; SOCS3 blocks insulin by impairing phosphorylation of insulin receptors.[37,39,40] A treatment that would inhibit TLR signaling could be beneficial in preventing or improving insulin resistance.[41] C10 has already been proven to inhibit TLR3 signaling in Hashimoto's thyroiditis.[3] Phenylmethimazole (C10) inhibits the TLR4 signaling pathway, making it a promising novel therapeutic for reversing both leptin and insulin resistance and thus possibly in the treatment of obesity and T2DM.[42,43]

Discussion

There are already multiple pharmacologic compounds used to treat T2DM. Each acts to overcome some part of the pathophysiology of T2DM (Table 1). Often these compounds are used in combination to attack the various abnormalities seen with T2DM. The newer compounds discussed in this paper have the potential to be used in the treatment of obesity and T2DM, but unfortunately they will not be available in the near future. Specific ghrelin antagonists, 11β-HSD1 inhibitors, and TLR receptor inhibitors may also prove to be safe and effective for the treatment of obesity and T2DM. However, in addition to clinical efficacy, the cost of these newer drugs will be a major limiting factor in their clinical use, especially in the economically at-risk populations discussed here. Keeping this in mind, Glucophage (*generic*, metformin; Bristol-Myers Squibb, Princeton, NJ), one of the most commonly used oral agents is on the $4 generic list at many pharmacies but is still too expensive for some budgets. Thus, affording diabetes medications is another stressor coupled with food insecurity, which promotes the cycle of socioeconomic stress.

Table 1 Examples of some of the existing drugs for T2DM

Class	Therapy target	Examples
Biguanides	Gluconeogenesis	Glucophage
Thiazolinediones	PPAR-γ	Rosiglitazone* Pioglitazone
Sulfonylureas	Beta cells—insulin secretion	Glipizide Glyburide Glimepiride
α-glucosidase inhibitors	α-glucosidase in the brush border of the small intestines	Acarbose
DPP-4 inhibitors	Dipeptidal peptidase type 4	Sitagliptin
Glucagon-like peptide-1 mimetic	Synthetic glucagon-like peptide-1	Exenatide†
Meglinitides	Beta cells—insulin secretion	Repaglinide Nateglinide

*Rosiglitizone (Avandia, GlaxoSmithKline, London, UK) has had bad press recently and is not frequently used as of this writing.
†Exenatide (Byetta, Amylin Pharmaceuticals, San Diego, CA) is injected, whereas the rest of these medications are taken orally.

Conclusion

Visceral obesity, T2DM, and their associated cardiovascular complications are major health care concerns. Lower socioeconomic status, stress from poverty, and food insecurity are major contributors to the development of obesity and T2DM. In addition to adequate food for nutritional requirements, finding affordable interventions for these at-risk populations must be a national priority to avoid the personal crisis of poor or declining health and the stress of trying to afford healthy foods and medications. As more is discovered about the physiology of stress and its role in the development of chronic diseases like diabetes, perhaps more therapy can be targeted at the underlying causes along with preventive medicine measures such as diet and exercise.

Acknowledgments

We acknowledge Kelly McCall, PhD, Leonard Kohn, MD, and Shelby Mullins.

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