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Brief Historical Perspective

THE CONCEPT OF LEPTIN RESISTANCE appeared in the literature almost as soon as the hormone itself was discovered. For purposes of our discussion, leptin resistance will be defined as, “reduced or absent responsiveness to the feeding and body weight inhibitory effects of the hormone in obese individuals in comparison with normal (lean) controls.” Two early reports, demonstrating significant correlations in humans between circulating leptin levels and increasing adiposity, came to the conclusion that resistance to the purported regulatory role of leptin on appetite and body weight must be induced as levels of the hormone increase (18, 43). In short order, the concept of leptin resistance was given experimental support by the finding of decreased ratios of cerebrospinal fluid vs. plasma levels of leptin in obese humans (14, 61). Parallel findings were made at almost the same time in obese rodents (24, 73). Whatever its mechanism, the notion of leptin resistance provided a ready explanation for excess body fat in individuals in the face of extremely high circulating leptin levels. Despite rather compelling initial observations, the notion of leptin resistance remained controversial at early stages of its advancement (4), or was reinterpreted in terms of individual variability in genetically determined leptin response thresholds (56). In fairness, these reviews appeared prior to experimental evidence demonstrating the existence of leptin resistance in obese humans (28, 31, 44). Moreover, findings of significant associations between leptin receptor gene polymorphisms and body mass index, fat mass, and eating behavior in humans were subsequently published (15, 21, 69). Nevertheless, it was not until experimental demonstrations of the phenomenon in outbred animals and subsequent analyses of the biological mechanisms involved that the notion gained widespread acceptance.

Experimental leptin resistance was first demonstrated in wild-type mice made obese on a high-fat (HF) diet (13). This was followed by numerous reports of leptin resistance in diet-induced obese rodent models in response to central and/or peripheral administration of leptin (25, 70, 72). More careful behavioral analysis of the sequence of events in the induction of diet-induced leptin resistance revealed what appeared to be a two-step process over successive weeks of HF feeding, with the expression of first peripheral, and then central, leptin resistance (23, 39). Parallel work on potential biological mechanisms underlying leptin resistance revealed the saturation at elevated circulating leptin levels of an active blood-brain barrier (BBB) leptin transport mechanism (7, 12), reduced hypothalamic leptin receptor expression (42, 66), and the inhibition of hypothalamic leptin receptor signal transducer and activator of transcription-3 (STAT-3) second messenger signaling (23) in HF-fed animals. Evidence indicates that these biological events may well parallel the behavioral sequence described above in the induction of leptin resistance (23, 38). Newer observations have confirmed earlier findings of leptin receptor downregulation and reduced leptin binding at hypothalamic sites (32, 40), and additional work has expanded our understanding of the second messenger alterations underlying central leptin resistance. Thus, two intracellular inhibitory factors have been identified (9, 74), suppressor of cytokine signaling-3 and protein tyrosine phosphatase-1B, which reduce leptin receptor signaling by preventing activation of or dephosphorylating the janus-kinase component of the receptor, respectively. These discoveries have permitted a more sophisticated analysis of second messenger mechanisms potentially contributing to central leptin resistance when circulating leptin levels become elevated (29, 52). Leptin resistance is today recognized as a significant contributor to obesity with interest focused on its potential role in the onset vs. maintenance of the obese state (3, 45, 59).

The New Finding and Its Significance

Now comes a report from Shapiro et al. (60) of a hitherto unsuspected form of leptin resistance based on dietary administration of a high concentration of fructose. Basically, outbred Sprague-Dawley rats fed a 60% fructose diet (by weight) for 6 mo failed to reduce 24-h food intake in response to intraperitoneal leptin administration in contrast to a control group consuming an equicaloric 60% starch diet for the same period of time. Lack of response in the fructose-consuming group was associated with an ~26% reduction in hypothalamic STAT-3 phosphorylation. Subsequent exposure of previously fructose-fed rats to a HF diet resulted in 65% greater body weight gain over a 2-wk period, in comparison with body weight gain in HF-fed control rats. Moreover, serum triglyceride (TG) levels in the fructose-fed rats were positively correlated with the reduced anorectic response after leptin injection and with degree of body weight gain when the rats were placed on the HF diet. These results are remarkable for several reasons. First, two of the hallmarks in the induction of diet-induced leptin resistance are elevated body weight (primarily fat) levels and increased circulating leptin concentrations. In the current study, after 6 mo of fructose feeding, circulating leptin levels,
body weight, and body fat of the fructose-fed group were identical to those of the control group. This alone renders the phenomenon a unique form of diet-induced leptin resistance. Second, leptin resistance induced by fructose feeding led to a pronounced susceptibility to increased weight gain on an already potent obesity-inducing 60% HF diet. Third, as the authors note, fructose-induced leptin resistance has the characteristics of a “silent” form of the phenomenon, remaining undetectable (with one exception) by standard measures of food intake, body weight gain, and serum hormone and metabolite levels, until a HF diet is made available to previously fructose-fed rats.

The one exception, elevated circulating TG in the fructose-fed rats even prior to exposure to the HF diet, appears, however, to provide us with both a potential marker for this syndrome and to cast light on the probable mechanism underlying this phenomenon. As the authors note, Banks et al. (6) have previously shown that elevated serum TGs reduce BBB leptin transport in rats. Indeed in this experiment, the investigators (6) demonstrated acute in vivo leptin resistance in rats for leptin transport across the BBB in response to intravenously infused TG. This observation is thus consistent with leptin resistance accompanying elevated TG in the fructose-fed rats of the current study. Alternatively, as the authors also note, fructose may directly reduce STAT-3 signaling in brain, as suggested by earlier results obtained in peripheral (hepatic) tissue (55). However, it is unclear whether fructose has access to hypothalamic tissue, since this form of hexose cannot cross the BBB (47, 50). Whether one or both of these mechanisms is involved can, of course, be readily tested by examining the effects on feeding and weight gain of peripheral vs. central leptin injections in fructose-fed rats. In addition, cerebrospinal fluid levels of leptin in fructose-fed rats can be sampled and compared to levels in controls (see Ref. 73). If such tests reveal that the leptin resistance induced by fructose is based exclusively on TG-mediated impairment of leptin transport across the BBB, with no additional induced hypothalamic defect, then this adds to the uniqueness of the phenomenon as a form of diet-induced leptin resistance.

A survey of the existing literature reveals further clues that impaired transport at the BBB may indeed be an explanation for the current results. Two studies (37, 71) examined the rapidity of onset of leptin resistance in HF-fed rats and noted that HF diet-induced leptin resistance for feeding inhibition occurred after only brief intervals of HF diet access (3–5 days). In the case of the former study (37), leptin resistance occurred prior to any significant body weight change. In both cases, the authors came to the conclusion that dietary fat may induce leptin resistance within a short period of time. Unfortunately, TG levels were not measured in either study. To be sure, onset of leptin resistance on HF diets is not always this rapid (23, 68) and is probably dependent, not only on the percent and composition of the fat and carbohydrate components of the diet, but also on strain and environmental conditions (10, 30). Nevertheless there is reasonable evidence to support the hypothesis of TG-mediated fructose-induced leptin resistance. This notion undoubtedly would come as no surprise to Banks (5), who suggested that BBB-based leptin resistance may, in fact, be the major form of the phenomenon in humans. What is perhaps surprising about this phenomenon to investigators familiar with leptin resistance protocols is its simplicity, uniqueness, and prolonged effects on HF diet-induced weight gain.

Is the Phenomenon Specific To Fructose?

As the above discussion implies, major questions exist concerning the specificity of this effect for the sugar fructose. To address these, several crucial control conditions should accompany the next demonstration of fructose-induced leptin resistance, including parallel groups of rats consuming equal and greater amounts of glucose and sucrose (which itself contains a glucose and a fructose moiety), such that both total control sugar and total fructose intake are calorically equated. In addition, one would also want to test the effects of feeding high concentrations of TG-promoting dietary lipids, such as long-chain fats; although, in this case, increases of TG level associated with leptin resistance would have to be demonstrated prior to any elevation of leptin levels and body fat. If such dietary sugar and fat feeding tests prove positive, then fructose-induced leptin resistance would have to be considered one example of TG-induced leptin resistance, nonetheless informative and replete with clinical implications. The issue of fructose-induced body weight gain also comes to bear here. In spite of the induction of leptin resistance, feeding of a high concentration of fructose in the diet resulted in no differential body weight gain in fructose-fed rats in the current study (60). However, other workers have observed fructose-induced body weight gain in rodents when fructose was offered in solution or as a component of the diet (34, 46). These latter results are more consistent with the establishment of leptin resistance and raise the issue of under what conditions fructose-induced leptin resistance remains “silent.” Is it as simple as a concentration of dietary fat in the fructose-containing diet that fails to cross the threshold for the expression of leptin resistance? Or is dietary fat providing some other essential leptin-inhibitory signal? Finally other sugars, such as sucrose, are known to elevate circulating TG and induce body weight gain and obesity in rodents (1, 35). Thus, in studies seeking to demonstrate carbohydrate-induced leptin resistance, whether specific to fructose or not, care must be taken to distinguish between leptin-resistant effects based on TG elevations per se vs. those in which elevated adiposity and/or leptin levels may potentially be involved.

One irony about the present finding is that it involves the feeding of fructose, a form of sugar present in both fruits and processed foods associated with potentially pathogenic peripheral metabolic effects (11, 33). The irony, of course, is that in this case (60), we have a hitherto unsuspected but demonstrably detrimental effect of fructose based directly on its effects on brain. However, given the multiple peripheral metabolic and hormonal effects of fructose (27), one might reasonably ask whether peripheral mechanisms stimulated by fructose may independently attenuate the effects of injected leptin. Thus a recent human study demonstrated that fructose consumed with meals, in contrast to glucose, not only elevated circulating TG, but failed to reduce postprandial ghrelin levels and also lowered circulating levels of insulin and leptin, all effects that would be expected to reduce satiety (65). These results have been questioned, however, in several additional studies in which not only hormone and metabolite levels, but also satiety responses following administration of fructose and other sugar
Implications of the Finding

Leptin resistance is relatively easy to establish in rodents, and the study of its experimental determinants and underlying mechanisms has advanced rapidly. In contrast, studies demonstrating human leptin resistance and its effects are few indeed. Such studies have almost exclusively been correlational, examining the relationship between leptin levels and adiposity (16, 36, 69) or have been focused on specific metabolic or behavioral effects of leptin in lean vs. obese individuals (41, 57, 64). In short, our knowledge of the extent of and mechanisms underlying human leptin resistance is fragmentary at best. It should be noted that studies of leptin resistance in obese humans would require experimental administration of high doses of the hormone, and would necessitate both FDA and sponsor approval. Needless to say, such studies would be both risky and costly. The opportunity now presents itself to induce leptin resistance in humans with a relatively simple procedure limited to safe and reversible nutritional manipulations. In principle, lean subjects could be used in such studies, although individuals at risk for obesity would be of more interest. Leptin doses required for testing would be considerably smaller. The way has already been paved with numerous studies of the effects of fructose and other sugars on hormonal and appetitive responses in human subjects. Most of these studies have utilized short-term fructose and other sugar administration. However, the Shapiro et al. study (60) suggests that longer dietary intervention may be required. This may be based on the more sustained TG elevations characteristic of high carbohydrate feeding, which tends to increase very low-density lipoprotein TG concentrations (51). Nevertheless, studies examining the required time of onset, specific nutritional determinants, and behavioral effects of carbohydrate- or fat-induced leptin resistance in humans appear feasible. Note that the concept of insulin resistance was well known before safe and effective techniques for its measurement were developed (20, 26, 48, 49). The value of finding a specific protocol that reliably induces leptin resistance in at least some individuals would be considerable. First, it would permit an examination of the extent and characteristics of human leptin resistance. For example, are both the appetite- and energy-expenditure-altering effects of leptin compromised in the leptin resistance state, and, if so, do these deficits occur simultaneously (see Ref. 58)? Second, if elevated circulating TG can be shown to be a reliable marker of leptin resistance in humans, the role of leptin resistance in the onset and maintenance of obesity can potentially be investigated, and rational interventions based on this knowledge can perhaps be designed. Finally, if dietary fructose can itself be identified as one cause of leptin resistance, this result would undoubtedly add to the long list of warnings issued concerning the use of fructose in the human diet. We eagerly await further developments arising from this exciting finding.

REFERENCES


