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Correspondence

Is leptin the causal factor of the changes in food intake observed after glucocorticoid infusion?

To the Editor,

I read the interesting study of Askari et al in the recent issue of *Metabolism* [1], and although I found the protocol very clever, I am quite concerned about their interpretation of the data. They found that increasing leptin concentration via a continuous intravenous infusion of hydrocortisone in humans during 24 hours was associated with a decrease in energy intake and, more specifically, in carbohydrate and fat intake. In the discussion they attribute this effect on food intake to leptin, based on the well-known satiety effect of centrally or peripherally administered leptin [2-4]. I agree that there is a body of evidence that leptin is involved in eating behavior. We have, for example, found with my colleagues that plasma leptin concentration at the onset of the meal and energy intake is negatively related [5,6]. However, I consider difficult to infer a role of leptin in the intake data of the present study for several reasons. First, it is clear in Fig. 1 that the glucocorticoid infusion produced a sustained elevation in plasma glucose concentrations as soon as 1 hour after its start. Before each meal, glucose concentration was higher in the hydrocortisone than in the placebo condition, reaching a 40% difference before dinner and a level of 180 mg/dL after dinner. It is now well established for 25 years [7] that glucose is a major determinant of meal onset, and this has been repeatedly shown in humans by other laboratories [8-10]. The neurophysiology of this central role of glucose has been quite extensively described [11] since the first work of Oomura and his team [12]. In a previous study, food intake not motivated by hunger was the only one situation where there was not the classic glucose preprandial profile [6]. In this latter case, the amount of food intake was moreover consistently lower although leptin levels were not different. In the study by Askari et al, hunger was unfortunately not assessed. Moreover, it is striking that plasma leptin levels did not increase before the eighth hour, although intake at lunch was lower 4 hours earlier. Thus, it is not reasonable to conclude that leptin is the causal factor of this change in food intake without any procedure maintaining glucose level constant among conditions. It is also not reasonable to attribute a macronutrient specificity to this reduction in food intake. We have analyzed and demonstrated in a previous study [13] how an apparent macronutrient specificity of an anorexic agent could be an artifact because of the place of the macronutrient in the meal. Only if this bias is taken into account can authors conclude to a possible macronutrient specificity. Usually, exploring macronutrient choice requires specific studies with procedures of conditioning as previously described [14,15]. In conclusion, the role of leptin in the results of the study of Askari et al should be taken with great caution, and data would have gained to be interpreted in the light of the mechanisms discovered in this area during the last century.

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Response to the letter to the editor by Chapelot

To the Editor,

Dr Chapelot makes interesting comments regarding our observation on energy adaptation to glucocorticoid-induced hyperleptinemia [1]. Indeed, plasma glucose levels increased modestly, especially during meal times, after hydrocortisone (HC) infusion, as was indicated in our article. In designing the study, we considered measures that would minimize the expected glucose excursions in response to glucocorticoid exposure. Infusing insulin to clamp plasma glucose was not an option because insulin is a leptin secretagogue [2,3]. On the other hand, fasting the study subjects to dampen glucose excursions was equally untenable because that would have abolished the leptin response to glucocorticoid [4,5].

It is thus possible, as argued by Dr Chapelot, that preprandial plasma glucose levels could have contributed to the modulation of food intake observed during HC infusion. It must be noted though that the data showing modulation of hunger by preprandial blood glucose levels are most persuasive in animal models [6]. Among humans, hyperphagia persists in patients with diabetes despite ambient hyperglycemia. The latter indicates that any inhibitory effect of plasma glucose levels on food intake in humans must be quite modest or easily overridden. As described in the article [1], the subjects in our study were approached repeatedly and offered meals and snacks ad libitum. The results obtained from such a study design may be quite different from one in which patients request meals in response to hunger. We regret that a subjective hunger scale was not administered to the subjects in our study, as that would have helped clarify whether food intake was in response to hunger or other cues. In addition, the point regarding macronutrient specificity is well noted.

Clearly, multiple behavioral, metabolic, neural, and peripheral factors are involved in the regulation of food intake in humans [7]. Circulating leptin levels and ambient glycemia are but two of these numerous regulatory factors.

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