Author's response to reviews

Title: Diet Induced Weight Loss Increases Satiety in Obese Women

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Author's response to reviews: see over
Reviewer: Stylianos Nicolaidis

Response to major issue #1:

“The cohort in question has reached a new set point and this is why negative A comes earlier than on the first test. That is OK; but, why does A come earlier and not as in the first test, when the subjects were also at their (by that time, under the M regimen they were consuming) set point?”

The referee hits an important point. The whole story is focused on the set-point precisely because what is changed is NOT the initial rating, but the time course of onset of negative alliesthesia. We interpret earlier onset of negative alliesthesia as indicative of a lowered setpoint. For instance in various experiments on alliesthesia we have shown that when we provide subjects with an ad-libitum bland diet, they lose weight and show an earlier onset of alliesthesia than in pre-diet conditions. Classically, earlier onset of negative alliesthesia confirms that the setpoint has been lowered by some mechanism, in this case, the new dietary regimen.

Response to major issue #2:

“The subjects reached a new SP; The present SP is being defended under the new conditions, ie the new M regimen. Should we understand that, in order to maintain this new SP these subjects must continue consuming permanently this new artificial regimen?

The answer is yes.

We believe the lowering of the set-point was induced by the diet. Previous studies have shown that diets that have a low glycemic index (Slabber, Barnard, Kuy, Dannhauser, & Schall, 1994; Spieth, Harnish, Lenders, Raezer, Pereira, Hangen, & Ludwig, 2000; Ball, Keller, Moyer-Mileur, Ding, Donaldson, & Jackson, 2003; Ebbeling, Leidig, Sinclair, Hangen, & Ludwig, 2003; Ludwig, 2003; Roberts, 2003), are rich in calcium ((Teegarden, Lin, Weaver, Lyle, & McCabe, 1999; Zemel, Shi, DiRienzo, & Zemel, 2000; Lin, Lyle, McCabe, McCabe, Weaver, & Teegarden, 2000; Carruth & Skinner, 2001; Zemel, 2003; Parikh & Yanovski, 2003) or relatively high in protein may favor a negative energy balance. The Mincavi diet combines these three factors. It is possible that they have played a role in the lowering of the set-point.

What if they returned to their usual one?

We believe that they would probably gain the weight back.
In the present case subjects were at their SP before the beginning and also, the authors believe, at the end of the M regimen. Shouldn’t they display the same, not a shortened A? Another argument that would better convince the reader would be provided by a “control” group where the subjects would follow the same series of tests, same timing etc but, either they would not loose weight or would not follow the treatment at all between the two tests. Such a control can be justified because one could expect the changes in A could be related merely to the subject’s previous experience of having passed the testing procedure once before (ie “schedule-induced” learning). Add to that the 40 S reward.”

Our data show that the new dietary composition favors a lowering of the setpoint. Once subjects achieve their new lowered setpoint, and a balance energy intake is achieved at the new setpoint, subjects will maintain it as long as they consume a similar diet. Unfortunately in this study at three months it is presumptuous to extrapolate beyond this time point without data. We have shown in later experiments on setpoint and satiety in morbidly obese patients who undergo bariatric bypass a stable body weight correlates with a lowered setpoint for body weight up to six months post surgery (manuscript submitted international journal of bariatric surgery). In our bariatric study we included unoperated morbidly obese control subjects. In unoperated controls, setpoint increased slightly, as did time to achieve negative alliesthesia over a six month period. We are satisfied that there is no learning effect in our design particularly since subjects showed the same level of pleasurable rating on first stimulus at first visit and again at three months. This suggests that the rating of sweet sensation was unaltered by the regime, yet surprisingly the satiety kinetics were lower for each subject after lowering weight.

From our experiment it can be inferred that this dietary regimen favors a lowering of the body weight setpoint. Lower setpoint occurred over three months and this could also be maintained or further lowered provided the regimen is also maintained. One of the key variables that remain to be explored is the effect of using a moderate weight loss approach versus a significantly dropping body weight by ultra low calorie diet over a few days.

We have modified the manuscript in accordance with the above. In summary the revised manuscript clearly indicates in the Discussion Section, an accurate reference to the mentioned bariatric surgery control group (submitted manuscript) as well as an updated Figure 5.

Suggested minor changes:

P 3 the word “equilibrium” may be misleading. It is used in chemistry and has a precise meaning. It could be replaced by “balance”.

We have accepted the reviewer’s suggestion and modified the sentence. It now reads “Energy balance is dependent upon a constant interchange between the energy intake and energy expenditure”.

P 3 The idea of exteroceptive (cephalic and post-cephalic) stimuli affecting internal regulatory processes was well shown in the 60ies.
Designated “anticipatory reflexes” (NY Acad Sci 1969) they prepare, at a preabsorptive stage the classic postabsorptive processes (neuroendocrin).

We thank the reviewer for the helpful reference and have added it to the appropriate section of the manuscript. “Nicolaïdis, S. (1969): "Early Systemic Responses to Orogastric Stimulation in the Regulation of Food and Water Balance: Functional and Electrophysiological Data," Ann. N.Y. Acad. Sci., 157, 1176-1203”.

P 5 “creating survival curve”. Explain or give reference.

The mention of survival curve was removed. The sentence now reads “In order to follow the time course of satiation in our experimental groups, we analyzed the data using the product limit method of Kaplan-Meier”. Appropriate reference to the data analysis is included in the revised manuscript.

P 9 “food intake of 1800 to 2400 kc/d depending on energy needs”. Who measured these energy needs?

Caloric needs were adjusted on an individual basis as prescribed by the dietary regimen. Dieticians match the caloric needs to participants according to lifestyle and job requirements (i.e. sedentary lifestyle vs. active laborer). The sentence was modified and now reads “A dietician assigned each participant a food plan providing either 1400, 1800, 2000 or 2400 kc/d (5852 to 8360 kJ/d) depending on their BMI, age and level of physical activity. During the “weight loss phase” participants are assigned one of the four diet plans that range from 1400 to 2000 kcal/d”. 
Reviewer: Eric Doucet

Major Compulsory Revisions

“1- The fact that the authors used satiety and negative alliesthesia interchangeably is of some concern. As stated by the authors in their introduction, satiety is a term coined to define a state when food intake is generally terminated because of a number of feedback cues. Although the reviewer does not disagree with the notion that people generally stop eating when a food becomes displeasurable, the fact that the two terms are equated in this paper needs to be better defended. Because very little food was consumed during the alliesthesia tests, this reviewer does not understand why the authors referred to satiety to describe their main finding. Further, meals generally present more variety than one single item. Can it then be assumed that because one particular item becomes less pleasurable, all others would be perceived the same way? It is suggested that, unless the argument can be better defended, the authors change their title and not use these 2 terms interchangeably in the text.”

The reviewer agrees with accepted definition of satiety and satiation. Then if follows that the introduction also defines the process by which a pleasant stimulus (e.g. candy) can in certain experimental conditions become unpleasant. And if repeatedly ingested the same pleasant stimulus leads to cessation of intake (e.g. satiety) or negative alliesthesia. The lead author has defended this notion for a number of years. It also follows that the two terms are closely related. The line where satiety and/or negative alliesthesia occurs is undeterminable since they are the same. Therefore we use the terms interchangeably.

The author suggests that since participants consumed little food the term satiety is not appropriate. We disagree with this notion. Participants arrived fasted overnight to our laboratory. We are satisfied that repeated ingestion of the sweet stimuli lead to displeasure and a desire to stop the experimental session. We interpret this as satiety. We agree that the dietary variety seen in free ranging diet studies was not present, but the experiment aimed at the kinetic for hedonic rating of the repeated ingestion of stimuli.

It can be assumed that we could produce a kinetic for a lipid or a protein stimuli. The difficulty in discerning which of the dietary constituents plays the lead in ending intake would be difficult if we used a varied diet. However, our terminology would not change if this was the case as we would expect the pleasurable rating to change with each repeated stimuli.

“2- It is now well known that weight loss causes changes in peptides (and neuropeptides) known to impact on energy intake and expenditure. Without going into the details, these changes have been shown to favor anabolism (increase energy intake and decrease in energy expenditure). Further, these results become apparent early into the energy restriction process even without any noticeable changes in body weight or
composition. This being said, how do the authors reconcile their results with this increasing pool of published data. One wonders whether the observed differences rather resulted from changes in macronutrient preference, or more specifically a change in sweet preference that could have arisen from the nutritional education obtained over the course of the weight loss program. Although the authors partially addressed this issue in the discussion and even cite papers that have indeed shown changes in taste preferences, they need to further modify this section.”

Changes in sweet preference was not the underlying cause in our experiment. The initial rating of pleasure remained the same at first visit and again at three months. This confirms that there was no shift in sweet preference. The change in kinetic follows the lowering of the setpoint by the dietary regimen.

“3- In the opinion of this reviewer, the paper needs to be more focused on the main research question. Although the sections on set-point theory are interesting and important for the background of the paper, they should be limited to this section. The main research question of this paper did not address the issue of the set-point theory.”

We have revised the entire manuscript and included a control obese group in Discussion (new Fig. 5). The entire manuscript benefits from the inclusion of such data. The stability of the setpoint in non-dieters adds significant proof to our results.

“4- The discussion needs some attention. For example, the sections on ghrelin and calcium do not seem to add anything to the main finding of this study.”

The discussion section was rewritten in the light of the above. Particular attention should now be focused on the introduction of control group data.

**Minor Essential Revisions**

1-When addressing the set-point theory, some mention of down-regulation in heat production should be made.

Reference to Leblanc et als.’ results has been added to the manuscript

2-If the reviewer understood correctly, subjects were measured before and after a 3 mo. intervention. How then can the authors allude to «better weight maintenance» at the end of the eight paragraph of the discussion?

The discussion was re-written and this has been removed from the revised manuscript.

3-Could carbohydrate reserves (on this relatively high-carbohydrate diet) have influenced the main outcome of the study?

No, since subjects rated the initial pleasure of the sweet stimulus equally pleasurable before and after the dietary intervention.
Discretionary Revisions

1-This reviewer applauds the inclusion of classic studies throughout the manuscript. It is suggested that the re-analysis of Minnesota semi-starvation study by Keys also be cited in the introduction.

Reference to the re-analysis of the Keys (1950) Minnesota semi-starvation study by Dulloo et al. (1996) has been inserted into the introduction section of the revised manuscript.