Commentary

MOLECULAR METABOLISM

Ceramide sensing in the hippocampus: The Lipostatic theory and *Ockham's razor*☆

Cristina Contreras[1,2], **Miguel López**[1,2,*]

Despite the indisputable evidence that regulation of food intake and energy expenditure is highly complex [1], there is a basic principle in science known as *Ockham's Razor,* which states that "*among competing hypotheses, the hypothesis with the fewest assumptions should be selected*". More than 70 years ago, it was proposed that the central nervous system (CNS) sensed circulating levels of metabolites, such as glucose, lipids and amino acids, generated in proportion to body energy stores or nutritional status, and that feeding (and in a larger extend, energy balance) was modified according to the levels of those molecules. This led to the formulation of the *Glucostatic, Lipostatic* and *Aminostatic Hypotheses* [2]. The discovery of leptin and its receptors, however, provided a strong molecular basis for homeostatic energy control, decreasing the relevance of the *Lipostatic Hypothesis*. However, even with the discovery of leptin and a broad range of other hormonal regulators of food intake [1], the concept behind the *Lipostatic* or other the nutrient-based hypotheses was never fully ruled out. During the 1980s, compelling evidence demonstrated the anorectic effect of peripheral lipid emulsion treatments [3]. The specific molecular nature of the signal molecule remained elusive until recently when, in a series of elegant experiments, *Rossetti*, *Lam and colleagues* demonstrated that central administration specifically of long chain fatty acids (LCFAs) inhibits food intake and additionally modulates insulin secretion, hepatic glucose production and lipogenesis [4].

In spite of this evidence, so far, the lipid sensing theory is basically a "*Hypothalamocentric*" concept, where the hypothalamus is the *most important brain area for sensing and regulating peripheral metabolism*. Therefore, it is highly interesting that in this issue of *Molecular Metabolism*, *Magnan and colleagues* provide elegant proof that in the hippocampus (a brain region that belongs to the limbic system and is traditionally known for its involvement in the modulation of memory) lipoprotein lipase (LPL, the enzyme that hydrolyzes triglycerides in lipoproteins) acts as a lipid sensor and, importantly, that this action is critical in the control of energy balance [5]. Neuronal LPL has been related to synaptic remodeling, as demonstrated by impaired learning and memory function in LPL deficient mice [6]. A current study has also reported that neuronal LPL is involved in the modulation of energy homeostasis. Neuronal LPL null mice show hyperphagia and obesity, an effect associated with expression of orexigenic neuropeptides in the hypothalamus (namely, agouti related protein, AgRP, and neuropeptide Y, NPY) and decreased metabolic rate [7]. Bearing in mind that hippocampal lesions lead to body weight gain [8] and that LPL is highly expressed in the hippocampus when compared with other brain areas [6], *Magnan and colleagues* tested the possibility that hippocampal LPL might play a role in the regulation of energy homeostasis. Using pharmacological and genetic approaches, they show that inhibition of hippocampal LPL promotes feeding-independent weight gain, as well as decreased locomotor activity and energy expenditure, in association with reduced parasympathetic tone [5]. Of note, the effect of LPL inhibition was related to increased *de novo* ceramide synthesis in the hippocampus. In order to test the mechanistic relationship of both events, they blocked ceramide synthesis in a LPL null background by using central administration of myriocin. Their data show that myriocin efficiently prevented the gain in body weight associated with decreased hippocampal LPL activity. Again, this reversion of the phenotype occurred independent of changes in food intake [5].

The relevance of these findings is intriguing and opens up several questions that will require further investigation. First of all, what is the exact mechanism of hippocampal LPL actions of energy balance? Some possibilities can be speculated on. Alterations in LPL function in the hippocampus might be implicated in the cognitive impairment related to pathologically increased food consumption [9], however, this possibility seems unlikely, as the observed phenotype shows feeding-independency. The reduction in energy expenditure after LPL inhibition is also of interest: does it depend on decreased locomotor activity? This possibility also seems improbable, since recent data have demonstrated that, below thermoneutrality (the experiments of this study were carried at 22 ± 1 °C), changes in activity do not drive changes in total daily energy expenditure [10]. Therefore, the cause of the observed decrease in energy expenditure remains unclear. In this regard, the activation of parasympathetic tone may be of relevance. It is well known that facultative thermogenesis is centrally regulated; brown adipose tissue (BAT) uncoupling, as well as liver and muscle oxidation are controlled by the hypothalamus through the autonomic nervous system [11]. However, in the current scenario, involvement of BAT thermogenesis is doubtful, since BAT mainly receives sympathetic input. Considering the key role of

[1]Department of Physiology, *NeurObesity* Group, CIMUS, University of Santiago de Compostela-Instituto de Investigación Sanitaria, Santiago de Compostela 15782, Spain [2]CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Santiago de Compostela 15706, Spain

*Corresponding author at: Department of Physiology, *NeurObesity* Group, CIMUS, University of Santiago de Compostela-Instituto de Investigación Sanitaria, Santiago de Compostela 15782, Spain. Tel.: +34 881 815420; fax: +34 881 815403. Email: m.lopez@usc.es (M. López).

Received December 13, 2013 • Revision received December 19, 2013 • Accepted December 20, 2014

http://dx.doi.org/10.1016/j.molmet.2013.12.004

parasympathetic innervation in the control of liver function [11], reduced hepatic oxidation as a result of central LPL inhibition may be a possibility. Vagotomy experiments will help to answer this question.

Finally, the most challenging part of this study is exploring the role of hippocampal ceramides in the modulation of energy balance. Ceramides comprise a family of simple sphingolipids generated from fatty acid and sphingosine [12]. While ceramides are present at low levels within biological membranes and in the circulation, they make important contributions to cell membrane structure and cell signaling pathways [12]. In this sense, the concept that a lipid species in low abundance, such as ceramides (about 1% of the dry weight in the human brain), may be sensed in discrete brain areas, such as the hippocampus, to regulate global energy homeostasis is quite provocative. This concept brings us back to the classic Lipostatic Hypothesis, which should be then expanded from including abundant circulating energy storing lipids, such as fatty acids, to uncommon, signaling lipids, such as ceramides. Still, the molecular mechanism through which hippocampal ceramides mediate their effects is unresolved. An interesting possibility may be endoplasmic reticulum (ER) stress. Increased ceramide production can lead to lipotoxicity and ER stress, a mechanism underlying insulin resistance and liver disease [12]. Recently, hypothalamic ER stress has also been described as a pathophysiological mechanism leading to obesity [13]. Whether increased ceramide synthesis after LPL inhibition may induce ER stress in the hippocampus and subsequent positive energy balance will require further investigation. However, if correct, this hypothesis would permit the integration of lipid sensing and impaired cellular function in two different brain areas, namely the hypothalamus and the hippocampus, which could eventually increase our possibilities for therapeutic intervention in the future.

In summary, the current study of *Magnan and colleagues* adds further confirmation that lipid sensing (in a broader context) in different areas of the brain is a key pathophysiological mechanism leading to obesity. In addition, their data present scientific evidence to our daily feeding experience and the fact that lipids modulate appetite. Moreover, this confirms again that 8 centuries ago *William of Ockham* was right.

ACKNOWLEDGMENTS

The authors thank *Dr. Silje Skrede* and *Dr. Johan Fernø* (University of Bergen, Norway) for their comments and criticisms. This work has received funding from the *European Community's Seventh Framework Programme* (FP7/2007–2013) under Grant agreement no. 281854 – the *ObERStress European Research Council Project* (ML), *Xunta de Galicia* (ML: 2012-CP070) and *Instituto de Salud Carlos III* (ISCIII; ML: PI12/01814). *CIBER de Fisiopatología de la Obesidad y Nutrición* is an initiative of ISCIII.

CONFLICT OF INTEREST DISCLOSURE

Authors declare no conflict of interest.

REFERENCES

[1] Sohn, J.W., Elmquist, J.K., Williams, K.W., 2013. Neuronal circuits that regulate feeding behavior and metabolism. Trends in Neurosciences 36 (9):504–512.

[2] Lopez, M., Tovar, S., Vazquez, M.J., Williams, L.M., Dieguez, C., 2007. Peripheral tissue–brain interactions in the regulation of food intake. Proceedings of the Nutrition Society 66 (1):131–155.

[3] Woods, S.C., Stein, L.J., McKay, L.D., Porte, D., Jr., 1984. Suppression of food intake by intravenous nutrients and insulin in the baboon. American Journal of Physiology 247 (2 Pt 2):R393–R401.

[4] Yue, J.T., Lam, T.K., 2012. Lipid sensing and insulin resistance in the brain. Cell Metabolism 15 (5):646–655.

[5] Picard, A., Rouch, C.K.N., Moullé, V.S., Croizier, S., Denis, R.G., Castel, J., et al., 2014. Hippocampal lipoprotein lipase regulates energy balance in rodents. Molecular Metabolism , http://dx.doi.org/10.1016/j.molmet.2013.11.002.

[6] Wang, H., Eckel, R.H., 2009. Lipoprotein lipase: from gene to obesity. American Journal of Physiology – Endocrinology and Metabolism 297 (2):E271–E288.

[7] Wang, H., Astarita, G., Taussig, M.D., Bharadwaj, K.G., DiPatrizio, N.V., Nave, K.A., et al., 2011. Deficiency of lipoprotein lipase in neurons modifies the regulation of energy balance and leads to obesity. Cell Metabolism 13 (1):105–113.

[8] Davidson, T.L., Kanoski, S.E., Schier, L.A., Clegg, D.J., Benoit, S.C., 2007. A potential role for the hippocampus in energy intake and body weight regulation. Current Opinion in Pharmacology 7 (6):613–616.

[9] Kanoski, S.E., Hayes, M.R., Greenwald, H.S., Fortin, S.M., Gianessi, C.A., Gilbert, J.R., et al., 2011. Hippocampal leptin signaling reduces food intake and modulates food-related memory processing. Neuropsychopharmacology 36 (9):1859–1870.

[10] Virtue, S., Even, P., Vidal-Puig, A., 2012. Below thermoneutrality, changes in activity do not drive changes in total daily energy expenditure between groups of mice. Cell Metabolism 16 (5):665–671.

[11] López, M., Alvarez, C.V., Nogueiras, R., Diéguez, C., 2013. Energy balance regulation by thyroid hormones at central level. Trends in Molecular Medicine 19 (7):418–427.

[12] Bikman, B.T., Summers, S.A., 2011. Ceramides as modulators of cellular and whole-body metabolism. Journal of Clinical Investigation 121 (11):4222–4230.

[13] Zhang, X., Zhang, G., Zhang, H., Karin, M., Bai, H., Cai, D., 2008. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell 135 (1):61–73.

