

The AMPK-Malonyl-CoA-CPT1 Axis in the Control of Hypothalamic Neuronal Function

Dear Editor,

We would like to offer alternative perspectives to those suggested in a recent article in *Cell Metabolism* on the potential roles of FAS, malonyl-CoA and CPT1 in hypothalamic function. In Lopez et al. (2008) the fasting- and ghrelin-mediated (AMPK-dependent) downregulation of FAS expression was proposed to be “an adaptive mechanism that helps to prevent malonyl-CoA from decreasing to deleteriously low levels in the hypothalamus.” We suggest that the downregulation of FAS serves to prime neurons to respond to re-feeding by enabling a more rapid increase in [malonyl-CoA] when feeding signals reach the hypothalamus; this would control meal size more efficiently. The rationale for a CPT1C-associated signaling role for malonyl-CoA independently from its inhibition of CPT1 activity is not supported by existing data. CPT1C (the activity of which is difficult to detect in vitro even with the use of sensitive radiochemical assays, owing to its extremely low catalytic constant [Sierra et al., 2008]) binds malonyl-CoA with the same affinity as CPT1A (Price et al., 2002). We have suggested that it could buffer the availability of malonyl-CoA in specific micro-environments within the cell (Price et al., 2002). Malonyl-CoA is capable of signaling indirectly through its inhibition of the highly active isoforms CPT 1A and/or 1B; such inhibition raises the concentrations of cytosolic long-chain acyl-CoA (LC-CoA) esters, potentially making CPT 1 activity central to neuroendocrine cell responses, as these metabolites are (1) activators of the K^+ _{ATP} channels and therefore able to affect neuronal electrical activity, and (2) sensitizers of vesicular (neuro)peptide secretion.

In (Lopez et al., 2008) correlations were drawn between short-term changes in CPT activity measured in vitro, and tissue malonyl-CoA content measured in the VMH. However, during assay of CPT activity, the malonyl-CoA would have been infinitely diluted in tissue extracts and assay media. However, mechanisms that specifically enable CPT1A (not 1C) to adapt its sensitivity to malonyl-CoA inhibition to different physiological conditions, coincident with changes in cellular [malonyl-CoA], do exist and amplify the effects of changes in the concentration of the inhibitor in vivo; see Zammit (1999) for review. More generally, these mechanisms are also likely to be important in adapting the function of CPT1A-expressing hypothalamic neurons to factors such as dietary fat composition, obesity, and fasting, as they do in other cell types in which CPT1A is expressed. Similarly, the modulation of CPT1A sensitivity to malonyl-CoA through altered mitochondrial outer membrane composition (Zammit, 1999) has the potential to be involved in the reported attenuation of the CPT1A-mediated anorexigenic signal in rats maintained for 3 days on a high-fat diet (Pocai et al., 2006).

The high CPT activity measured in the VMH by Lopez et al. (2008) using a colorimetric assay was correlated with the immunoquantification of only one (CPT1C) of the three isoforms of CPT1 that are expressed in the hypothalamus (Price et al., 2002). Owing to the very low intrinsic catalytic activity of CPT1C, it is highly likely that the activity measured was due to CPT1A and/or CPT1B, whereas immunoquantification was specifically of CPT1C protein. This discrepancy may require a re-evaluation of some of the data presented. The absence of an effect of icv

etomoxir alone on food intake in Lopez et al. (2008) differs from previous observations (Pocai et al., 2006), namely that icv-delivered pharmacological and antisense oligomer-mediated specific inhibition of hypothalamic CPT1A results in a rapid inhibition of food intake and hepatic glucose production. This discrepancy suggests that the exact site of icv delivery may determine the an/orexigenic response, depending on which precise cell types are affected and on which CPT1 isoform(s) are expressed therein. It is also possible that opposite directions of changes in CPT 1 activity, and thus of [acyl-CoA], are required for activation/inhibition of the electrical activity of particular types of neurons. We hope that a thorough appreciation of the metabolic principles involved in the regulation of the AMPK-malonyl-CoA-CPT 1 axis may improve our understanding of hypothalamic neuronal function in response and adaptation to dietary signals.

Victor A. Zammit^{1,*}
and Arduino Arduini²

¹Clinical Sciences Research Institute, Warwick Medical School, University of Warwick, CV4 7AL, UK

²Iperboreale Pharma srl, R&D Department, 66020 San Giovanni Teatino, Italy

*Correspondence: v.a.zammit@warwick.ac.uk

DOI 10.1016/j.cmet.2008.07.009

REFERENCES

Lopez, M., Lage, R., Saha, A.K., Perez-Tilve, D., Vazquez, M.J., Varela, L., Sangiao-Alvarellos, S., Tovar, S., Raghay, K., Rodriguez-Cuenca, S., et al. (2008). *Cell Metab.* 7, 389–399.

Pocai, A., Lam, T.K., Obici, S., Gutierrez-Juarez, R., Muse, E.D., Arduini, A., and Rossetti, L. (2006). *J. Clin. Invest.* 116, 1081–1091.

Price, N., van der Leij, F., Jackson, V., Corstorphine, C.C., Thomson, R., Sorensen, A., and Zammit, V.A. (2002). *Genomics* 80, 433–442.

Sierra, A.Y., Gratacos, E., Carrasco, P., Clotet, J., Urena, J., Serra, D., Asins, G., Hegardt, F.G., and Casals, N. (2008). *J. Biol. Chem.* 283, 6878–6885.

Zammit, V.A. (1999). *Biochem. J.* 343, 505–515.