Invited Commentary

Comment on Christiansen *et al.*: When food met pharma

First published online 24 August 2015

Fatty acids can affect a variety of cell and tissue functions, so influence physiology and modify disease risk[1]. It is generally considered that many of the functional effects of fatty acids rely upon their incorporation into cell membranes from where they influence membrane fluidity, membrane protein function, lipid raft formation, intracellular signalling and the generation of bioactive lipid mediators[2,3]. Incorporation of fatty acids into cell membranes involves their covalent linkage into more complex lipids like phospholipids. However, the discovery of cell surface receptors that can bind fatty acids has raised the possibility that fatty acids could regulate cell and tissue function from the extracellular space and in the non-esterified form. Four such free fatty acid (FFA) receptors are known; these are all G-protein-coupled receptors (GPR). FFA2 receptor (GPR43) and FFA3 receptor (GPR41) bind SCFA, whereas FFA1 receptor (GPR40) and FFA4 receptor (GPR120) bind long-chain saturated and unsaturated fatty acids. FFA1 receptor is expressed in pancreas, brain and taste buds, whereas FFA4 receptor is expressed in intestinal cells, pancreas, brain, adipocytes and macrophages. These expression patterns suggest that the FFA1 and FFA4 receptors may be involved in fatty acid regulation of dietary fat intake, hormone release, hormone responsiveness (e.g. insulin sensitivity) and inflammation. Indeed Oh *et al.*[4] demonstrated that FFA4 receptor was key to the ability of the *n*-3 PUFA DHA in promoting insulin sensitivity in adipocytes and in reducing inflammatory responses of macrophages. The recognition that fatty acids can act in a direct receptor-mediated fashion calls for new approaches in the study of their functional effects and of the mechanisms involved.

In a paper recently published in the *British Journal of Nutrition*, Christiansen *et al.*[5] adopted a purely pharmacological ('pharma') approach in the study of the metabolic effects of fatty acids. They screened a wide range of medium- and long-chain saturated and unsaturated fatty acids, including arachidonic acid, EPA and DHA and their precursors, and also a number of unusual *cis*, *trans*, oxidised and branched fatty acids, for activity towards FFA1 and FFA4 receptors by performing detailed concentration-response curves using reporter assays. The outcomes were described in terms of potency (defined as the concentration required to elicit 50 % of the maximum response) and efficacy (defined as the maximum response elicited compared with that seen with lauric acid). Relatively, few fatty acids were selective for one FFA receptor over the other, but many showed greater activity towards one of the receptors than towards the other. Among the PUFA studied, the *n*-6 PUFA linoleic, γ-linolenic, di-homo-γ-linolenic, arachidonic and adrenic and the *n*-3 PUFA α-linolenic and EPA were very active towards the FFA1 receptor, whereas γ-linolenic, di-homo-γ-linolenic and stearidonic acids were very active towards the FFA4 receptor. The γ-linolenic-acid analog, pinolenic acid (5, 9, 12–18 : 3*n*-6), was the most potent dual agonist of both FFA1 and FFA4 receptors among the fatty acids tested. Pinolenic acid is found naturally in Korean and Siberian pine nut oils, where it contributes as much as 20 % of the fatty acids present. Christiansen *et al.*[5] studied pinolenic acid further. It was active towards both human and mouse FFA1 and FFA4 receptors and was compared with authentic selective agonists for each receptor in concentration-response reporter assays, which confirmed its strong activity towards both receptors. Finally, acute administration of pine nut oil, pinolenic acid or pinolenic acid ethyl ester, was demonstrated to result in a lower blood glucose response to an oral glucose challenge in mice compared with maize oil, suggesting an improved metabolic response.

The strength of the work of Christiansen *et al.*[5] is its detailed evaluation of concentration-dependent responses, an approach common in the pharma world but rarer in nutrition science. Too many *in vitro* or animal studies of nutrients and food-related non-nutrients fail to evaluate the influence of several concentrations of the compound under study, seriously reducing their value. Dose–response studies are more difficult to perform in humans, but studies evaluating the dose-dependent incorporation of *n*-3 PUFA have been reported[6,7] as having dose–response studies, evaluating the effect of *n*-3 PUFA on blood lipids[8], platelet reactivity[9] and inflammation[10]. Such studies are valuable because they can identify thresholds for intakes that elicit a desired biological effect and above which no further effect is seen. Furthermore, description of dose or concentration dependence makes the report of any biological effect more robust and establishes greater evidence for a 'cause and effect' relationship between the provision of the food, food component or supplement and the biological outcome that is reported. Establishing such 'cause and effect' relationships through dose- or concentration-response studies can be a vital element in the process of substantiating a health claim. Therefore, nutrition science would be wise to adopt practices more akin to pharma when evaluating the functional properties and health impacts of foods, nutrients and non-nutrient food components. In fact, in this context the boundaries between 'food and pharma' are now somewhat blurred[11,12], with the pharma industry becoming increasingly interested in food components as functional agents and the food industry and nutrition scientists being increasingly

expected to adopt pharma practices as part of their normal research and development activities. This blurring of the boundaries is likely to become greater over the next years, and will certainly increase the chances of new discoveries being made by both the food and pharma industries and of translating those discoveries into new products, new claims, new preventative strategies and new treatments for human disease.

Philip C. Calder[1,2,3]

[1]*Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, UK*

[2]*NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, UK*

[3]*Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia*

email pcc@soton.ac.uk

doi:10.1017/S0007114515002809

References

1. Calder PC (2015) Functional roles of fatty acids and their effects on human health. *J Parent Ent Nutr* (In the Press).
2. Calder PC (2012) Mechanisms of action of (*n*-3) fatty acids. *J Nutr* **142**, 592S–599S.
3. Calder PC (2015) Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. *Biochim Biophys Acta* **1851**, 469–484.
4. Oh DY, Talukdar S, Bae EJ, *et al.* (2010) GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* **142**, 687–698.
5. Christiansen E, Watterson KR, Stocker CJ, *et al.* (2015) Activity of dietary fatty acids on FFA1 and FFA4 and characterisation of pinolenic acid as a dual FFA1/FFA4 agonist with potential effect against metabolic diseases. *Br J Nutr* **113**, 1677–1688.
6. Katan MB, Deslypere JP, van Birgelen AP, *et al.* (1997) Kinetics of the incorporation of dietary fatty acids into serum cholesteryl esters, erythrocyte membranes, and adipose tissue: an 18-month controlled study. *J Lipid Res* **38**, 2012–2022.
7. Browning LM, Walker CG, Mander AP, *et al.* (2012) Incorporation of eicosapentaenoic and docosahexaenoic acids into lipid pools when given as supplements providing doses equivalent to typical intakes of oily fish. *Am J Clin Nutr* **96**, 748–758.
8. Harris WS, Windsor SL & Dujovne CA (1991) Effects of four doses of *n*-3 fatty acids given to hyperlipidemic patients for six months. *J Am Coll Nutr* **10**, 220–227.
9. von Schacky C, Fischer S & Weber PC (1985) Long-term effects of dietary marine omega-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. *J Clin Invest* **76**, 1626–1631.
10. Rees D, Miles EA, Banerjee T, *et al.* (2006) Dose-related effects of eicosapentaenoic acid on innate immune function in healthy humans: a comparison of young and older men. *Am J Clin Nutr* **83**, 331–342.
11. Calder PC (2011) Fatty acids and inflammation: the cutting edge between food and pharma. *Eur J Pharmacol* **668**, S50–S58.
12. Calder PC (2013) Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? *Br J Clin Pharmacol* **75**, 645–662.