agree with Hedge et al[1] that one of the most important questions is whether sufficient quantities of Δ^{12}-PGJ_3 are formed in vivo to exert any biologic activity. Here, we comment on this eminently crucial issue from pharmacologic and nutrition perspectives.

PGJ_3 and PGJ_2 are the dehydrated products of PGD_3 and PGD_2 formed in vivo from eicosapentaenoic acid (EPA) and arachidonic acid (ARA), respectively, by the catalytic action of cyclooxygenase (COX). PGJ_3 and PGJ_2 are further dehydrated and isomerized to produce Δ^{12}-PGJ_3 and 15d-PGJ_3 and 5d-PGJ_2, respectively. Common feature of Δ^{12}-PGJ_3 and 15d-PGJ_2 is the highly reactive cyclopentenone ring, which is readily attacked by low- and high-molecular-mass thiols to form thioethers (Figure 1). Thiolation of Δ^{12}-PGJ_3 and 15d-PGJ_2 is likely to reduce both availability and bioactivity of Δ^{12}-PGJ_3 and 15d-PGJ_2. So far, there are no data about excretion of Δ^{12}-PGJ_3 and 15d-PGJ_3. We (Figure 1) and others[3] found only pM-concentrations of 15d-PGJ_2 in human urine, while PGJ_3 metabolites including 15d-PGJ_3 were below the detection limit of our method (30 pM) in urine. This may suggest that basal PGJ_3 biosynthesis from EPA is several fold lower than PGJ_2 from ARA. Dietary EPA has been shown to increase formation of prostaglandin I_3 (PGI_3) and thromboxane A_3 (TxA_3), but EPA, even at very high doses, did not increase PGI_3 and TxA_3 synthesis to a degree comparable with that of PGI_2 and TxA_2 from ARA.[4]

Δ^{12}-PGJ_3 and 15d-PGJ_2 are considered potentially useful therapeutic agents for the treatment of cancer.[1,2] Dietary EPA supplementation is unlikely to produce nM-concentrations of Δ^{12}-PGJ_3 required for antileukemic activity, but topical administration of considerable amounts of synthetic Δ^{12}-PGJ_3 would be required.

Dimitrios Tsikas
Institute of Clinical Pharmacology, Hannover Medical School, Hannover, Germany

Dirk O. Stichtenoth
Institute of Clinical Pharmacology, Hannover Medical School, Hannover, Germany

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Correspondence: Prof Dimitrios Tsikas, Institute of Clinical Pharmacology, Hannover Medical School, Carl-Neuberg-Str 1, 30625 Hannover, Germany; e-mail: tsikas.dimitros@mh-hannover.de.

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Response:

Endogenous levels of D12-PGJ3 derived from eicosapentaenoic acid

In response to the comment by Tsikas and Stichtenoth,[1] we would like to provide clarification for their views and address the questions. First, while it is correct that the reactivity of the 2 electrophilic centers could make these classes of compounds less bioavailable, our data clearly demonstrates that intraperitoneal administration of D12-PGJ3 completely eradicates leukemia stem cells in the bone marrow and spleen. This suggests that the formation of Michael adducts does not affect their antileukemic activity nor systemic bioavailability. Second, it is not surprising to find that the pM concentrations of 2- and 3-series CyPGs (of the J class) in the urine. Our studies show (see Figure 1 in Hegde et al[2]) that macrophages cultured with 50μM EPA for a week, produce D12-PGJ3 in the cell culture media in quantities (nM) sufficient to target leukemia stem cells. The authors show very low levels (pM) of these metabolites in urine. However they did not measure levels in the serum and it would be difficult to infer serum concentrations from these measurements. Moreover, it is not surprising that given the low rate of conversion, the level of D12-PGJ3 from ARA-derived EPA is likely to be in the pM range as described. In the future, quantitation of these metabolites in the serum will be necessary to provide a true measure of their concentration, particularly in EPA-supplemented individuals. Unpublished studies from our laboratory confirm the metabolism of dietary EPA generates D12-PGJ3 at concentrations in the serum high enough to induce apoptosis in leukemia stem cells in vitro. A manuscript with these results is being currently prepared for submission.

K. Sandeep Prabhu
Center for Molecular Immunology and Infectious Disease and Center for Molecular Toxicology and Carcinogenesis, Department of Veterinary and Biomedical Sciences, The Pennsylvania State University, University Park, PA

Robert F. Paulson
Center for Molecular Immunology and Infectious Disease, Department of Veterinary and Biomedical Sciences, The Pennsylvania State University, University Park, PA

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Correspondence: K. Sandeep Prabhu or Robert F. Paulson, Department of Veterinary and Biomedical Sciences, The Pennsylvania State University, 115 Henning Bld, Shortlidge Rd, University Park, PA 16802; e-mail: ksprabhu@psu.edu or rfp5@psu.edu.

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