LETTER

Some More Comments on 'Folate Deficiency in Chronic Pancreatitis'

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Dear Sir,

The comprehensive review by Braganza and Dormandy on micronutrient therapy for chronic pancreatitis included emphasis on the role of methyl group and thiol metabolism [1]. I am writing to expand on the comments expressed in the letter by Rajesh *et al*. [2] and the reply by Dr. Braganza [3] in the July issue of JOP. Journal of the Pancreas (Online). These have served to highlight the results reported by Girish *et al*. in which they suggest that a deficiency of methyl groups may be a factor in the development of pancreatitis [4]. In their letter, Rajesh *et al*. cite our paper showing that pancreatic secretion in rats is compromised in folate deficiency [2]. There is a close relationship between folate and methyl group metabolism. Folate is required for the *de novo* synthesis of methyl groups. The ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH) is regulated by the enzyme glycine N-methyltransferase (GNMT) under the control of a specific form of folate [5]. GNMT is very abundant in the exocrine cells of the pancreas [6] and in a subsequent publication we showed that SAM plays an important role in the secretory process from pancreatic exocrine cells [7]. In that paper we provided evidence that SAM might be needed for carboxymethylation of G proteins that are needed in the process of exocytosis. It should also be noted that the process of exocytosis involves the fusion and regeneration of membranes that are generated in the Golgi and the rough endoplasmic reticulum [8]. Tissues that are actively involved in exocrine secretion may then have an increased requirement for synthesis of phosphatidylcholine, an important component of the plasma membrane. There are two pathways that are used for the synthesis of phosphatidylcholine. The major pathway in most tissues utilizes preformed choline reacting with cytidine triphosphate to eventually form phosphatidylcholine. The second pathway occurs primarily in the liver and message for it is present in other tissues including pancreas [9]. It involves the sequential methylation of phosphatidylethanolamine by the enzyme phosphatidylethanolamine N-methyltransferase (PEMT) [10]. Thus three molecules of SAM are used for each molecule of phosphatidylcholine synthesized. The decreased plasma methionine and increased homocysteine plus the reduced level of folate in these patients suggest a diminished ability to remethylate homocysteine in chronic pancreatitis as suggested by Girish *et al*. [4]. It would be of interest to measure plasma levels of SAM and SAH in this group of patients in order to determine whether decreased methylation may be the underlying reason for the pancreatitis. In addition, dietary supplementation with methyl donors, such as betaine [11] that have been used to treat patients with cystathionine-beta-synthase deficiency, may be of use in treatment of chronic pancreatitis.

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Abbreviations GNMT: glycine N-methyltransferase; SAH: S-adenosylhomocysteine; SAM: S-adenosylmethionine

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