International Congress Series 1297 (2007) 217–227

www.ics-elsevier.com

Protein intake and calcium absorption – Potential role of the calcium sensor receptor

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Abstract. Dietary protein induces calcium excretion but the source of this calcium is unclear. Evidence from short-term studies indicates that protein promotes bone resorption, but many epidemiologic studies do not corroborate this. Evidence is also mixed on whether protein promotes calcium absorption. Studies in animal models suggest that the aromatic amino acid components of protein, but not the branched-chain amino acids, may activate calcium sensor receptors in the gut and increase gastric acid production. The latter could enhance calcium absorption. We compared the impact of aromatic and branched-chain amino acids on changes in calcium excretion and on an index of calcium absorption in 30 healthy older men and women. A 5-fold increase in aromatic amino acid intake induced a greater increase in calcium excretion, calcium absorption, and serum IGF-1 than did a similar increase in branched-chain amino acids. These findings are consistent with the concept that the calcium sensor receptor mediates selected effects of dietary protein on calcium metabolism.

Keywords: Calcium excretion; Calcium absorption; IGF-1; Calcium sensor receptor; Humans

1. Introduction

Heredity, diet, and other lifestyle factors contribute to risk of osteoporosis. Of the dietary constituents, calcium and vitamin D have received the most attention, but there is growing evidence that dietary protein is also important.

The relation of protein intake to calcium and bone metabolism is complex. Dietary protein promotes production of IGF-1, a bone growth factor. Protein may promote calcium

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0531-5131/
doi:10.1016/j.ics.2006.08.002

absorption, as described below, but this is not a consistent observation and the mechanism(s) are not established in humans.

It has long been recognized that dietary protein induces calciuria [1–4]. Protein is metabolized to acidic residue in proportion to its sulfur-containing amino acid content. Acid loads become more difficult to excrete [5] as renal function declines with aging [6]. The resulting mild metabolic acidosis affects bone in several ways: it increases osteoclastic activity [7] and bone resorption [8], inhibits osteoblastic activity [9–13], and promotes bone resorption through direct physico-chemical effects at the apatite surface [14]. Thus, bone serves as a buffer and in the process of neutralizing acid arising from acidogenic diets, calcium is lost from bone. Sebastian reported that in postmenopausal women, neutralization of endogenous acid production with oral administration of potassium bicarbonate leads to decreased urinary calcium excretion and positive calcium balance [15]. In an earlier study, ingestion of acid dramatically increased urinary calcium and hydroxyproline excretion in healthy men.

Despite these challenges to calcium conservation, the net effect of increasing protein intake on bone in older subjects is not consistently negative and often in fact is observed to be positive. In the original Framingham cohort, elderly subjects in the highest quartile of animal and total protein intake had lower rates of bone loss from the femoral neck and spine than subjects consuming less protein [16]. In a controlled, 6-month intervention study, 20 g/day of supplemental protein improved hip bone mineral density in elderly patients with recent hip fractures [17]. Munger et al. [18] reported that higher total (and animal) protein intakes were associated with a reduced incidence of hip fractures in postmenopausal women. In contrast, a high animal to plant protein intake ratio has been associated with greater bone loss from the femoral neck and a greater risk of hip fracture in one study in women aged 65 years and older [19]. Higher total and higher animal protein intakes have also been associated with increased risk of forearm fracture in younger postmenopausal women [20].

The explanation for these discrepant observations is not entirely clear. The often observed positive impact of dietary protein on bone strongly suggests that protein is acting in ways that are not understood and that, at least under some circumstances, the positive effects of protein may outweigh the negative effects of its acid load on bone. It is important to have a more comprehensive understanding of the mechanisms by which protein affects bone. The potential mechanisms to be considered in this chapter include the possibilities that 1) the CaR, activated by the aromatic amino acid component of dietary protein, promotes calcium absorption either directly or indirectly (by stimulation of gastric acid production) and that 2) the CaR is involved in the increase in hepatic IGF-1 production that occurs with increasing protein intake.

2. Regulation of gastric acid production

Gastric acid is produced by the parietal cell. These cells are located on the fundus and body of the stomach. H^+ secretion is stimulated by three different pathways: the neurocrine pathway mediated by acetylcholine, the endocrine pathway mediated by gastrin, and the paracrine pathway, mediated by histamine. There is interdependency of these pathways, as illustrated by the observation that histamine H_2-receptor antagonists inhibit not only the