Reply to UN Das

Dear Sir:

We agree with Das that glucose ingestion was shown to improve memory performance within ~1 h of ingestion compared with a non-energy-containing placebo in a range of human and rodent populations (1). The strongest effects in humans are observed in elderly subjects and in those with existing memory deficits or relatively poor glucose regulation (2) and may be limited to declarative memory tasks (3), which are mediated by the medial temporal lobe and related structures (4). For instance, in the study that Das referred to, we found that the beneficial effects of glucose ingestion were most evident in healthy elderly subjects with normal fasting plasma glucose concentrations who had the poorest β cell function (5). Furthermore, we extended the glucose data by showing that other carbohydrate foods could also improve memory.

Several mechanisms have been suggested to explain the effects of glucose ingestion on memory performance. Das discussed some of these and presented another potential mechanism. One common hypothesis suggests that glucose ingestion may improve memory by increasing plasma glucose concentrations, leading to alterations in glucose uptake and utilization by the brain and ultimately to an increase in the glucose-mediated synthesis of acetylcholine in the hippocampus region (6). As mentioned by Das, research with rodents supports this hypothesis (7). Others have suggested that the insulin response to an increase in glucose may be responsible for the effects on memory (8). Das suggested further that insulin may improve memory by stimulating endothelial nitric oxide formation and inhibiting the synthesis of tumor necrosis factor α. Although each of these mechanisms may be involved in mediating the effects of glucose on memory, our work suggests that other mechanisms are also involved.

The important finding of our study, which Das failed to refer to, is that barley ingestion improved memory similarly to the ingestion of glucose and mashed potatoes even though it had a minimal effect on blood glucose. Although it has been commonly argued that blood glucose must increase to 8–10 mmol/L for memory to improve (9), we found that barley, which increased blood glucose to only 6.7 mmol/L, improved memory similarly to glucose and potatoes, which increased blood glucose to ~9.5 mmol/L. In addition, although not measured, we anticipate that barley would also minimally affect insulin concentrations (10). Consequently, the aforementioned mechanisms are unlikely to account for the memory-enhancing effects of barley. Instead, our data suggest that the provision of energy, independently of elevations in blood glucose, can improve memory.

The effects of energy ingestion on gut-mediated responses could explain our findings. Several gut peptides, including cholecystokinin (11), gastrin-releasing peptide, pancreastatin, and amylin (12), influence memory in rodents, likely via stimulation of ascending fibers of the vagus nerve (11). Furthermore, electrical stimulation of the vagus in human subjects improves declarative memory (13), and vagotomy decreases the memory-enhancing effects of glucose (14) and peripherally injected drugs (11). Thus, the ingestion of any energy source may improve memory by these mechanisms, independently of elevations in blood glucose. Importantly, this mechanism does not rule out the acetylcholine or insulin hypotheses, but instead suggests that carbohydrates affect cognition by more than one mechanism.

Our current work, examining the effects of protein, carbohydrate, and fat on memory performance, will increase our understanding of the effects of energy ingestion on cognition compared with the individual effects of each macronutrient.

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REFERENCES


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**LETTERS TO THE EDITOR**

**Dietary ratio of animal to vegetable protein and rate of bone loss and risk of fracture in postmenopausal women**

Dear Sir:

We reported recently in the Journal that in free-living elderly white women, bone loss and hip fracture rates were greatest in those consuming diets with the highest ratio of animal to vegetable protein content (1). Those diets represented diets with the highest ratios of animal to vegetable foods consumed. Because animal foods tend to be net acid producing and vegetable foods net base producing (2), our results support the hypothesis that diet-dependent net endogenous acid production (NEAP) is a risk factor for bone loss and hip fracture in elderly white women.

In an accompanying editorial, Heaney (3) offers comments that might lead some readers to discount our findings and interpretation. He contends that opponents of the use of animal products “have had a disproportionate effect both on public consciousness and on the agenda of nutritional science itself,” and that it “would be surprising if the study had not been influenced to some extent by currents in the larger society.”

To allay the concerns of Journal readers, we offer a public opinion we published before having had any reason to suspect our article would be interpreted by anyone as having been unduly influenced by animal activist press:

By referring to the American diet as “protein-rich,” and linking dietary protein’s acid yield to bone damage, [the article entitled] “Could Diet Attack Bones? It’s a Beef About Meat” [(4)] might lead some readers to believe that Americans are eating too much protein. In fact, the protein content of American diets is below the evolutionary norm for humans, and therefore may be overall nutritionally suboptimal. For bone, the problem may not be too much acid from protein, but too little acid-neutralizing base from those types of plant foods that are rich in base, such as roots, tubers, fruits, and vegetable fruits and leaves. The plant foods that Americans eat most are cereal grains, such as wheat and rice, which are unusual plant foods in that they yield acid, not base. To boot, grains crowd out base-rich plant foods from the diet, helped in that by all those empty-calorie foods Americans eat, such as refined sugars and separated fats. In the acid attack on bone, the beef therefore is not so much with meat, as with grain and empty-calorie foods.

Nevertheless, Heaney may prove to have been prescient in predicting that “it is virtually certain that [the article by Sellmeyer et al] will be used by some to ‘prove’ that animal protein is positively harmful.” But if some do so, it will be because they failed to recognize that our findings speak only to the ratio of animal to vegetable foods consumed, as indexed by the ratio of animal to vegetable protein in the diet, and not specifically to the absolute amounts of animal food or protein consumed. Our hypothesis is that the rate of NEAP is a risk factor for bone loss and hip fracture. In our study, the ratio of animal to vegetable protein consumed was used as a surrogate for that risk factor because animal foods are richer in acid precursors than in base precursors and because many vegetable foods are richer in base precursors than in acid precursors (2). It would not be inconsistent with our findings or hypothesis if large increases in total animal protein intake above the range consumed by our subjects reduced rates of bone loss and fracture if those increases were accompanied by appropriate increases in the intake of vegetable protein in the form of high-base-yielding plant foods.

Heaney also takes us to task for teaching the myth that sulfuric acid yields are higher from animal than from vegetable protein. That chastisement reflects an uncritical read of our paper, however, because we neither asserted nor implied such differential acid yields. Indeed, we are on record for taking pains to disabuse followers of that myth, to the extent of even supplying a table showing overlapping values of potential sulfuric acid yields for a wide variety of animal and plant foods (per gram protein) (5). Moreover, any differences in animal compared with vegetable yields of sulfuric acid that might be obtained are only part of the picture. Another part of the picture is the differential animal and vegetable yields of bicarbonate from nonprotein constituents of the food. Many plant foods (e.g., roots, tubers, leafy green vegetables, and fruit) are richer per gram protein in such bicarbonate precursors than are animal foods (2). As an index of the NEAP, the ratio of animal to vegetable protein consumed in whole-food diets reflects the differential animal compared with vegetable yields of bicarbonate as well as those of sulfuric acid.

Heaney contends that our findings are at odds with reports of a positive relation between animal protein intake and skeletal health, specifically citing the Framingham Osteoporosis Study by Hannan et al (6). However, the focus of our article was the association of the rate of bone loss (and hip fracture) with the ratio of animal to vegetable protein consumed, whereas Hannan...