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Letter to the Editor

Allometric Scaling: Comparison of Interspecies Nutritional Relationships and Requirements

Dear Editor:

In a recent commentary, "Experimental Evidence That (-)-Epicatechin and Anthocyanins Modulate Glucagon-like Peptide-1 Metabolism: Relevant for Humans?," Christian Heiss and Ana Rodriguez-Mateos (1) respond to an article by Cremonini et al. (2) that demonstrates that (-)-epicatechin and anthocyanin metabolites modulate glucagon-like peptide-1 (GLP-1) metabolism in C57BL/6J mice and GLUTag cells. In general, their comments are favorable to the findings of Cremonini et al. (2). However, they are ambivalent regarding the allometric scaling approach used to estimate dosages in mice from published human studies. They suggest that the utility of allometry for effective interspecies comparisons remains an open question for studies of bioactive compounds. Their argument stems from observations that interspecies differences in absorption, microbiome modifications, and metabolism may compromise anything gained from making an allometric correction.

Understanding mechanisms and processes related to chemical transformations of bioactive compounds is of obvious importance in animal model studies intended to translate effective dosages to humans. However, in contrast to ambivalence towards allometry, I suggest that, in the early stages of research directed at bioactive compounds, its use as a tool is essential, particularly when the goal includes defining doses related to putative or potential health benefits (3–6).

For example, it has been known for decades that the metabolic rate of animals exponentially scales with body mass or volume. The exponent is almost always <1, $>2/3$, and most often close to 3/4. A consistent feature is fractal-like networks that facilitate the flow of nutrients and their cellular influx, utilization, and efflux. All bioactive compounds utilize such networks during transport, actions, and metabolism (5). The 2/3–3/4 exponent emerges naturally from such networks, albeit corrections are needed for assessing ectotherms (i.e., temperature regulation issues) or factors, such as ease of oxygen saturation (7, 8). In this regard, the empirical evidence for allometry is now overwhelming. In addition to metabolic energy estimates, it is possible to scale related dietary factors to body mass (e.g., vitamin and mineral relative needs) over 5–6 orders of magnitude (9, 10). Moreover, mathematical proofs for allometric scaling consistent with fractal-like networks have been published and validated (5, 11).

The use of an allometric approach is particularly seminal from a nutritional perspective. It requires thinking beyond isometric dimensions and focusing on dynamic and metabolic parameters rather than static and anthropometric parameters. Further, ignoring allometric parameters results in conceptual errors. For example, comparison or extrapolation based directly on body mass suggests that the human dose may be 2800-fold or greater than those of an experimental animal model, such as a mouse ($70\ kg_{human} \div 0.025\ kg_{mouse}$). In contrast, using metabolic body size–based parameters, the estimated difference is 200–400-fold and not 2800-fold. For example, if q_0 represents the animal's metabolic rate, and M represents mass, then the ratio is better stated as $q_0 \sim (M_{human})^{3/4} \div q_0 \sim (M_{mouse})^{3/4}$ or $23.2_{human} \div 0.063_{mouse}$ over the same time—that is, ~368. This estimate relates directly to empirical estimates of basal metabolism or resting energy expenditure (REE). For example, a small adult mouse's daily REE is ~4–8 kcal (12). For a 70-kg human, the value for REE (13) is ~1400 kcal/d (women) to ~1500–1700 kcal/d (men) (i.e., a ratio of 200–400-fold, in keeping with estimates based on metabolic body size).

If the focus is on bioactive compounds that influence energy regulation, appetite, or energy expenditure (i.e., GLP-1, insulin, glucagon), the relationships will seldom be isometrically mass-related. Animals have evolved from similar evolutionary and ecological time frames. Mice and humans have approximately 30,000 genes, yet only about 1 in a 100 is unique (14). It is always best to use scaling approaches for heuristic assessments that recognize similar evolutionary and ecological time frames.

What about situations wherein metabolic strategies essential for the metabolism or turnover of a bioactive compound differ between species? Regarding the putative health-related benefits of the bioactive compounds, all are influenced to some degree by the dynamic aspects of metabolic body size. For example, as noted, one can predicate the human dietary requirements for vitamins based on what is known about the requirements for mice (9, 10).

Consider the need for ascorbic acid (mouse vs. human). The mouse has no dietary requirement for ascorbic acid. Nevertheless, the amount of ascorbic acid a mouse synthesizes per unit of food energy consumed is about the same as the human's dietary need for ascorbic acid on an energy basis (8, 9). Moreover, the turnover for ascorbic acid [a function related to $q_o \sim (\text{mass in kg})^{1/4}$] in humans may be estimated using data related to the turnover of ascorbic acid for the mouse (9, 10).

As a final point, interspecies differences in microbiome-related and secondary metabolism do have the potential of compromising "translational estimates of dose" based on allometry. Nevertheless, using an allometric protocol to scale a dosage for a bioactive compound that is effective in humans to the experimental model lets one know expeditiously whether potential problems may be due to differences in metabolism or related issues. Importantly, it opens the door to questions as to whether the experiment model or the diet chosen for the research question is appropriate. For example, phase I and II biotransformation enzymes play significant roles in the activation and turnover of many bioactive compounds. Rudolf et al. (15) have reported that, in response to flavone exposure, the levels of isoforms for cytochrome P450 monooxygenase and glutathione-S-transferase activity and expression can vary as much as 10–100-fold when a nutritionally complete but otherwise chemically defined diet is contrasted with a

conventional feed-pellet diet, or a diet fabricated to mimic the compositions of human diets (16).

In summary, given the extent to which allometric scaling applies to a broad range of phenomena, its application as a research tool should never be understated. Indeed, there is usually a good biological question to be answered when an organism deviates markedly from what seems to be a reasonable allometric-based prediction.

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