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Lipids and Lifespans: Constants and Contradictions

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With these unique data on echidna lipids, 'Tony' A.J. Hulbert and colleagues have added an important phylogenetic link to the allometric relationships of the polyunsaturated fatty acids (PUFAs) of membrane lipids to basal metabolic rate (BMR) and lifespan. Extensive studies in the past decade have developed the allometry of the membrane peroxidation index (PI), as calculated from the proportion of double bonds in fatty acids of membranes from heart and skeletal muscle. To a first approximation, a 25% decrease in PI from lower PUFA content doubles the lifespan.

According to chemical principles (limited data is cited), the relative numbers of double bonds in hydrocarbon chains predicts their oxidizability. The very long echidna lifespan was not predicted by the allometric relationship of lifespan on body size, but was predicted by the PI calculated for skeletal muscle or liver mitochondria. Hulbert's group has found these relationships throughout vertebrates and even invertebrates: the ultra-long-lived naked mole-rat vs lab mice (Mitchell et al 2008); birds (long-lived procellariiforms vs short-lived galliforms) (Buttner et al 2008); and bee castes (queen vs worker) (Haddad et al. 2007). All these 'comparisons' show inverse relationships of lifespan to the PI index.

Hulbert et al. have also probed these these relationships experimentally. Calorie restriction in mice, which increases lifespan, also lowered the PUFA content of muscle and the calculated PI, as predicted (Faulks et al 2006). Diet also has a major influence on the PUFA content and PI of honeybee castes (Haddad et al. 2007). Moreover, in vitro manipulation of levels of PUFAs in lipid bilayers ("species cross-over" experiments) caused corresponding changes in Na⁺K⁺ATPase and other key membrane activities (Hulbert, 2007). The biophysics involved is still speculative. The allometric matrix relating biochemical and metabolic parameters to lifespan and other whole animal (macroscopic) life history traits may get as close as biology can to having regularities like those in the Periodic Table of the Elements (Finch 1990, Chapter 5).

A contradiction arises about interpreting the PI from the naked-mole rat, which shows high levels of oxidation contrary to prediction. The naked-mole rat lives almost 10-fold longer than lab mice of the same size, just as predicted by the low PI for its size (Mitchell et al. 2007). Despite the calculated 2-fold lower lipid PI in most tissues, others reported that the naked-mole rat has 10-fold higher urinary isoprostanes and 2-fold or more oxidative damage to tissue DNA, lipids, and proteins than mice of the same age (Andziak et al 2006). The contrast of brain to the PI allometry of other organs, the importance of diet to tissue lipids, and the disconnect between the calculated PI and the observed levels of oxidative damage in some species are caveats for temperance in the joys of allometry. Of course, the level of oxidation is controlled by many processes beyond the lipid composition which are not represented by the PI.

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Moreover, the brain, however, deviates from the regularity of organ allometry in lipids and lifespans. Brain lipid PI is high across the mammals, mainly due to high levels of the highly oxidizable PUFA, docosahexanoic acid (DHA, 22:6 n-3) (Hulbert, 2006). DHA is 16% of the total phospholipid acyl chains in brain and has allometric coefficients on body size (M) that are very low relative to other organs: in brain, $DHA \sim M^{\text{exp}-0.01}$; in heart, $M^{\text{exp}-0.40}$ (Hulbert et al 2002). [this study did not include human brain data]. Humans are notable for lower synthesis of DHA than most mammals, and for the importance of dietary DHA to optimum somatic growth and cognitive development (Brenna, 2002; Finch and Stanford, 2004). In Alzheimer transgenic mice, DHA supplements lowered brain amyloid accumulation (Lim et al. 2005).

An important future goal is to understand species differences in lipid biosynthesis. Hulbert observes, correctly in my view, that peroxisomal enzymes which synthesize PUFAs (desaturases and elongases) merit comparative studies. Besides raw sequence comparative genomics of coding and regulatory sequences, I suggest looking at DNA methylation, which was just shown to mediate social caste differentiation (Kurcharski et al 2008) and thence the observed differences in lipid composition and predicted PI. There are also interesting questions about human evolution, the PUFA dietary intake and biosynthesis, and increased longevity (Finch and Stanford, 2004; Finch 2007): During the last 2–3 million years of human evolution, our ancestors changed gradually from plant-based diets to the global preference of *H sapiens* for meat-rich diets with high PUFA content (Finch and Stanford, 2004). And 30 years was added to the lifespan. Besides the evolved changes in apolipoprotein E isoforms which influence blood lipid composition, human fibroblasts have higher expression of the peroxisomal enzyme phytanoyl-CoA 2-hydroxylase (Karaman et al. 2003). Both genomic and lipidomic studies may give further insights about how humans evolved the longest primate lifespan.

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