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Perspectives on the membrane fatty acid unsaturation/pacemaker hypotheses of metabolism and aging

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ABSTRACT

The membrane pacemaker hypotheses of metabolism and aging are distinct, but interrelated hypotheses positing that increases in unsaturation of lipids within membranes are correlated with increasing basal metabolic rate and decreasing longevity, respectively. The two hypotheses each have evidence that either supports or contradicts them, but consensus has failed to emerge. In this review, we identify sources of weakness of previous studies supporting and contradicting these hypotheses and suggest different methods and lines of inquiry. The link between fatty acyl composition of membranes and membrane-bound protein activity is a central tenet of the membrane pacemaker hypothesis of metabolism, but the mechanism by which unsaturation would change protein activity is not well defined and, whereas fatty acid desaturases have been put forward by some as the mechanism behind evolutionary differences in fatty acyl composition of phospholipids among organisms, there have been no studies to differentiate whether desaturases have been more affected by natural selection on aging and metabolic rate than have elongases or acyltransferases. Past analyses have been hampered by potentially incorrect estimates of the peroxidizability of lipids and longevity of study animals, and by the confounding effect of phylogeny. According to some authors, body mass may also be a confounding effect that should be taken into account, though this is not universally accepted. Further research on this subject should focus more on mechanisms and take weaknesses of past studies into account.

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1. Introduction

One of the first hints that the fatty acyl composition of phospholipids could be systematically related to other important physiological parameters came with the observation that the amount of docosahexaenoic acid (DHA) attached to phospholipids in the heart was positively correlated with heart rate (Gudbjarnason, 1989). This observation motivated a series of studies that found that polyunsaturated fatty acid (PUFA) concentration in liver and muscle membranes was positively correlated with body mass in mammals and birds (Brand et al., 2003; Couture and Hulbert, 1995; Hulbert et al., 2002b,c). The amount of PUFA in membranes was also found to be positively correlated with the activity of certain membrane-bound proteins, such as Na+/K+-ATPase, and correlations between unsaturation index and proton leak were likely to be mediated through proteins, because the effects of changes in PUFA concentration on proton leak disappear when there are no proteins in a membrane (Brookes et al., 1998, 1997). It was hypothesized that these increases in protein activity may increase metabolic rate as well, thus leading to the membrane pacemaker hypothesis of metabolism (Brookes et al., 1998; Else and Wu, 1999; Hulbert and Else, 1999; Porter et al., 1996). This seminal series of studies spawned decades of research as it was a striking contrast to previous research on lipid–protein interactions, which studied specific lipid–protein interactions, rather than viewing lipids in a more generalized context (Hulbert and Else, 1999). Shortly thereafter, investigators showed that the level of unsaturation in mitochondrial membranes was negatively correlated with longevity in heart and liver from mammals (Pamplona et al., 2002a, 1999c, 1996; Portero-Otín et al., 2001), which led to the so called degree of fatty acid unsaturation (Pamplona et al., 2002a) or membrane pacemaker (Hulbert, 2005, 2003) hypotheses of aging. The two membrane pacemaker hypotheses, one connecting phospholipid fatty acyl composition to metabolic rate and the other connecting fatty acyl composition to longevity, are linked because metabolism and longevity are correlated with body mass and to each other (Hulbert et al., 2007). Unfortunately, these intercorrelations make it difficult to test the validity of each hypothesis separately. The correlations among level of unsaturation in membranes, longevity, and metabolic rate could be causally linked to one another or one or more of them could be separately related to body mass and not to each other.

Here, we discuss current evidence for and against the membrane pacemaker hypotheses of metabolism and aging and suggest changes that could be made to the lines of inquiry used to test these hypotheses. The mechanism by which the unsaturation of membranes could be connected to protein activity remains poorly defined in the literature on the membrane pacemaker hypothesis of metabolism. Additionally, it is unclear in species in which natural selection has brought about differences the unsaturation of membranes and, subsequently, in ageing and metabolic rate, whether natural selection was operating on desaturase activity, elongase activity, acyltransferase activity, or some combination of these enzymes. Experiments shedding light on these mechanisms would lead to a better understanding of these two hypotheses. Understanding would be further aided by adopting changes in the approaches used to study these hypotheses. For instance, the practice of combining fatty acid data from all phospholipid classes and all subcellular membranes could be obscuring differences that would help create a more nuanced understanding of mechanisms that influence metabolism and longevity, given that the fatty acyl composition of certain phospholipids, such as cardiolipin, appears to have a greater effect on oxidative stress and the activity of membrane proteins in the mitochondria than do other phospholipids (Aoun et al., 2012; Chicco and Sparagna, 2007; Hoch, 1992; Paradies et al., 2010a,b; Watkins et al., 1998). One method that would help solve this issue would be to use high-performance liquid chromatography coupled to mass spectrometry to quantify phospholipid species separately. Other difficulties with interpreting the conclusions of the current literature include potentially inaccurate measures of maximum lifespan and peroxidizability of lipids as well as a lack of consideration of the confounding factor of phylogeny. Body mass may also be a confounding factor, but correcting for body mass should be treated with some caution (Barja, 2014). Resolving mechanisms and being aware of these potential problems in future studies would help in determining validity of these two hypotheses.

2. Membrane pacemaker hypothesis of metabolism

Centered on several tenets, the membrane pacemaker hypothesis of metabolism suggests that a significant portion of basal metabolic rate is dictated by membrane-associated protein activity, such as the maintenance of chemical gradients in Na+ across the plasma membrane and protons across the inner mitochondrial membrane (Rolfe and Brown, 1997). Furthermore, the proportion of basal metabolic rate that these activities utilize is approximately the same in all organisms (Brand, 2000; Brand et al., 1991). Thirdly, unsaturated fatty acyl groups attached to phospholipids have physical properties that increase the activity of membrane-bound proteins and thus increase the metabolic rate of the whole organism (Turner et al., 2003). Therefore, species with more PUFA in their membranes will have higher mass-specific metabolic rates than those with a lower concentration of PUFA (Hulbert and Else, 2000; Sprecher, 2000).

Most of the evidence supporting this hypothesis comes from two sources: (i) correlations among the number of double bonds in a membrane, protein activity, and basal metabolic rate and (ii) experiments introducing proteins from one species into the membrane environment of a second species and *vice versa*. The unsaturation index, or mean number of double bonds in the fatty acyl groups of phospholipids in a membrane, and the percentage of DHA were positively correlated with metabolic rate, proton leak, and Na+/K+ ATPase activity within birds, within mammals, and among several ectotherms in liver, kidney, heart, and skeletal muscle (Brand et al., 2003; Brookes et al., 1998; Hulbert et al., 2002c; Porter et al., 1996; Turner et al., 2005c, 2003). Differences in unsaturation index and DHA concentration in the muscle mitochondria of rats, toads, and lizards were also correlated with differences in their mitochondrial oxidative capacities (Guderley et al., 2005). Furthermore, dietary manipulations in trout and genetic manipulations in mammals that increased the amount of PUFA in membranes increased mitochondrial activity or increased the activities of individual complexes in the electron transport chain (Guderley et al., 2008; Hagopian et al., 2010; Jaureguiberry et al., 2014). Experiments where Na+/K+ ATPase from rats and cattle was put into the less unsaturated membranes of toads and crocodiles exhibited a decrease in Na+/K+ ATPase activity. When the reverse experiments were done, Na+/K+ ATPase from toads and crocodiles exhibited increased activity in the more unsaturated membranes of rats and cattle, implying that the membrane environment of the Na+/K+ ATPase is at least partially responsible for changes in its activity levels (Else and Wu, 1999; Wu et al., 2004).

The membrane pacemaker hypothesis of metabolism, however, is not consistent with some data from intraspecific comparisons, with analysis that address the potentially confounding effect of body mass, and with comparisons of birds and mammals (Konarzewski and Książek, 2013). There was no correlation between metabolic rate and unsaturation index among individuals