

**ELEVATED FREE FATTY ACIDS (FFAs) – A COMMON DENOMINATOR FOR THE PROTECTED PHENOTYPES ASSOCIATED WITH CALORIC RESTRICTION IN RATS, LONG-LIVED MICE AND HIBERNATING SQUIRRELS.**

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Stressful events such as fasting, controlled caloric restriction (CR), and severe physical exercise initiate a rapid catabolic shift to lipolysis and ketogenesis that signal for the mobilization of FFAs and elevation of these factors in the circulation—a phenomenon that may also be associated with SIRT-1 expression. It is currently recognized that, in addition to their classic function as energy substrates, FFAs and their CoA-thioesters (CoAFFAs) also act as signaling molecules regulating ion channels, thyroid hormone synthesis and gene expression. Specifically, FFAs and their CoA-thioesters are the natural ligands to several nuclear receptors including PPARs, thyroid hormone receptor and hepatic nuclear receptor  $\alpha$ . We report here that the serum levels of total FFAs are elevated in two strains of rats subjected to 3 and 12 months of CR. In addition, in contrast to ad lib wild type, FFAs are also higher in ad lib dwarf mice, and both phenotypes upregulate FFAs in response to CR. Also, in contrast to euthermic controls, FFAs are significantly higher in hibernating squirrels. This association between hypoxia-tolerance during hibernation and elevated FFAs was further explored by examining FFA levels in neonatal rats. Free fatty acid levels were found to be elevated in 10d suckling animals when compared to weaned littermates—a transitional period associated with hypoxia-tolerance in the former and hypoxia susceptibility in the latter. Finally, the association between Sirtuins and the longevity of CR was explored by measuring the effects of FFAs on SIRT-1 expression in vitro. Our results show that these factors mimic the effects of CR serum on SIRT-1 expression. We, therefore, propose that FFAs act as an up-stream master mediator responsible for the protected phenotype and the longevity associated with CR models and the dwarf mouse, as well as for hypoxia – hypothermia tolerance observed in hibernating species.