The classical view of homeostasis considers a single range of biological capacities, extending above and below a 'normal' or mean value. Thus, we may consider mean blood pressure for an average 20 year old female to be approximately 110/70, with a high end ranging up to 130/80 and a low end ranging down to 100/60. Over the past two decades, however, studies from this laboratory (and several others) have demonstrated that cells, simple organisms, and even mammals, can temporarily expand the homeostatic range by undergoing transient adaptation. Such adaptive responses depend on altered gene expression and are orchestrated by signal transduction pathways, such as the Nrf2-Keap1 system. These adaptive pathways allow cells and organisms to cope with transient changes in (internal or external) environments, including many forms of stress. Thus, in addition to the 'normal' range of homeostatic capabilities, there is an additional range of adaptive capacity that I propose should be called, 'Adaptive Homeostasis.' Importantly, several studies from this laboratory now show that Adaptive Homeostasis declines with age in cells, worms, flies, and rodents; in other words, a decline in Adaptive Homeostasis appears to be a 'normal' age-dependent phenomenon. Declining Adaptive Homeostatic capacities may make older organisms (and people?) more susceptible to multiple stresses, and to disease. On the other hand, declining Adaptive Homeostasis may be protective against cancer – an example of Antagonistic Pleiotropy? While the full explanation for the age-dependent decline in Adaptive Homeostasis is still under study, our research indicates that diminishing Nrf2 responsiveness, and increasing levels of (competitive?) Nrf1, Bach1, and c-Myc may all play important roles.


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