LESSONS FROM THE PAST - HUMAN AND ANIMAL THERMAL PHYSIOLOGY

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Early attempts to establish the location of a thermoregulatory centre in the brain accounting for the stability of deep-body (core) temperature (T_c) in homeotherms found their first landmark in 1912 when Barbour using a water perfused thermode identified a heat-sensing centre driving T_c in the direction opposite to the change of thermode temperature. The emerging mono-centric concept of hypothalamic thermoregulation encompassing both control and thermosensory functions was supported by clinical and pathological studies and firmly cemented in the 60s with many classical quantitative thermode studies and by the discovery of warm sensitive hypothalamic neurons. Only in the late 60s theoretical considerations began to question hypothalamic thermosensitivity (HTS) as being too low to account for the known stability of homeothermic T_c, a problem initially overcome by proposing the classical hypotheses of adjustable set point control and of multiplicative interaction between skin and hypothalamic temperature. Also in the 60s the discovery of spinal cord thermosensitivity as well as of extrahypothalamic vestigial controller functions within the central nervous system (CNS) paved the way for studies establishing the multiple-input, multiple-controller concept of thermoregulation by identifying further extrahypothalamic sites of temperature signal generation, whose contributions, when integrated as deep-body thermosensitivity, were shown to closely match the thermosensitivity postulated to explain the known stability of T_c. Early monocentric studies of thermoregulation during exercise were confronted with the observation of reduced HTS requiring substantial non-thermal inputs as extra drives for heat defence. With the multiple-input concept this hypothetic non-thermal input substituting for the reduced HTS could be fully replaced by the contribution of extrahypothalamic thermosensors. Parallel to these studies ideas on neuronal temperature sensing have greatly advanced from viewing bimodal peripheral thermoreceptors and hypothalamic warm- and cold-sensitive neurons as the only relevant signal generators towards a verycomplex picture including monomodality of peripheral warm and cold thermoreceptors and multimodality of deep-body thermosensors. Our concepts on thermosensory specificity have radically changed, and today it appears that the deep-body temperature signal is only in part provided by thermoreceptive afferents, while its major fraction is generated by interneurons that are for the most part warm sensitive. Predominance of multimodality among neurons generating thermal inputs within the CNS seems to contribute to the interactions between thermoregulatory and other homeostatic control systems that are increasingly elucidated. Fever as a natural disturbance of homeothermia has been an important corrective for our understanding of how T_c is regulated. That febrile T_c changes are regulated was discovered as early as 120 years ago. Starting in the 40's with the important distinction between exogenous and endogenous pyrogens, research into the latter has continued to disclose multiple interacting cytokines driving many cellular and humoral host defence activities with prostaglandins being an important mediator between cytokines and hypothalamic targets generating febrile hyperthermia. Previous views of the organum vasculosum laminae terminalis as a monocentric, virtually exclusive blood-to-brain interface for fever mediation are changing and very recent data support a multiple input system involving vagal and somatic afferents as putative pyrogen sensors.

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