Are Black-Box Models of Thermoregulatory Control Obsolete? The Importance of Borrowed Knowledge

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Black-box models of thermoregulatory control have gained increasing importance in describing the properties of the biological thermostat and in devising working hypotheses for further experimental analysis. Incorporation of knowledge acquired independently from the systems analysis approach into black-box models of thermoregulation has proven useful in improving their predictive ability. The pieces of “borrowed knowledge” from independent analysis which are currently utilized in devising models of homeothermic thermoregulation comprise: (1) the proportional control property of the biological thermostat, (2) the Sherringtonian principles of synaptic interaction, (3) the multiple input control of thermoregulatory effectors with differential input-effector coupling, (4) the lack of significant thermosensory contribution from the hypothalamus in birds, (5) the existence of warm and cold receptors and the thermal characteristics of their responses, and (6) the Q10-type temperature dependence of temperature signal transmission within the central nervous system. Consideration of these pieces of borrowed knowledge has resulted in black-box models of temperature regulation in which explicit set-point terms are avoided.

For proponents of the “black-box” approach to physiological control processes, the active system of temperature regulation presents a particular challenge because of its complexity, due to the involvement of behavioral and numerous autonomic effectors. Systems analysis is one of several methodological approaches to elucidate the characteristics of those physiological processes by which the thermal state of a homeothermic organism and the states of activity of heat-generating, heat-conserving, and heat-dissipating mechanisms are interrelated. As emphasized by Grodins in 1968 [1], any cognitive approach of a human being to his material or immaterial environment involves that his ideas and prejudices, i.e., models in the widest sense, be checked against his perceptions and adjusted if necessary. The usefulness of constructing models as tools to describe or analyze the principles of temperature regulation has generally received critical support in previous discussions conducted in 1968 in New Haven [2] and in 1971 in Dublin [3].

Regulatory physiologists, when viewing a biological homeostatic system as a feedback system analogous to technical control devices, have become accustomed to speak conventionally of “black-box models,” if input-output relationships of homeostatic systems are described in mathematical form. According to early uses of the term “black box,” this view may be too restrictive. How the “black box” may have been originally conceived is indicated by Wiener’s description in the preface to the second edition of his book on cybernetics [4]. To illustrate his “black-box” conception, he

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makes use of the complementary term "white box" which, although quite elucidative, seems not to have found general use. The "black box" represents the real object of investigation, a device with input and output channels but unknown function and design. In connection with the empirical testing of its outputs generated by experimentally induced inputs, a "white box" may be constructed by the experimenter and progressively refined so as to reproduce the input-output properties of the "black box" as accurately as possible. The "white box" with its known internal design represents a model of the "black box" with its unknown internal design. The optimum accomplishment of the black-box approach, as defined in 1956 by Ashby [5] in his treatise on the black-box theory as a tool in science, would correspond to a perfect "black-box/white-box" relationship in terms of Wiener [4]. As a result, the same mathematical model would apply to the input-output coupling functions of both boxes, i.e., the relationship would be isomorphic in terms of set theory. According to Ashby [5] this isomorphism would define the equality—not identity—of the two boxes in such a way that if they were accidentally exchanged this exchange would be subsequently undetectable to the experimenter, irrespective of the fact that the internal networks, by which the identical input-output coupling functions are established, are completely different. Thus, the black-box theory does not consider the true design of the real object's internal network, but essentially reduces the study of the real world to a study of the flow of information.

According to the black-box theory, the ideal model for a biological homeostatic system would be an isomorphic mathematical expression. Most likely this could best be accomplished by a powerful digital computer with software developed so as to predict the output responses of the black box to all imaginable combinations of inputs with the highest degree of accuracy. For the thermoregulatory system, this approach was successfully pursued with the mathematical model presented as a FORTRAN program in 1968 by Stolwijk [6]. Its predictive ability could be improved by progressively optimizing the program operations. To do so without even asking whether the introduced calculations have anything to do with biological performances would be fully adequate. This fact, while not interfering with the great attractiveness of the isomorphic model from the viewpoint of applied science, is extremely disappointing for the enthusiast in basic science who not only wants to describe what a biological control system does, but also to know how the system does it. Moreover, the isomorphic model is generally far from what can be attained when dealing with biological input-output relationships. As a rule, their complexity is such that the control of all inputs and the analysis of all outputs is not possible. In general, the experimental limitations force us to lump a number of inputs together and, therefore, to achieve at best a presentation of a multitude of transformations by one or by a few, i.e., a homomorphic model in terms of set theory [5]. In addition, we usually have to assume a number of uncontrolled inputs to be more or less irrelevant for the system under consideration, i.e., the model is also incomplete and, thus, only approximately homomorphic. The classical additive [7] and multiplicative [8] models of hypothalamic temperature regulation present typical examples. Irrespective of their differences, they do not discriminate between cold and warm receptor inputs and consider hypothalamic temperature as representative of the entire thermal input from the body core. However, in the context of the black-box approach, these simplifications are fully adequate.

Consideration of knowledge obtained by independent methods about the components of biological control systems appears as a way to overcome the conceptual
limitations and to reduce the degrees of acceptable simplifications in the black-box approach as a tool in regulatory physiology without giving up its conceptual advantages. With regard to temperature regulation such independent knowledge would, for instance, consist of the results of studies concerned with the receptive components, with central nervous integration, and with the neural or humoral control of the autonomic and behavioral activities by which the organism reacts to disturbances of its internal or external environment. According to Ashby [5], these approaches provide "borrowed knowledge" about the inner design of the black box which may be used in designing the models of systems analysis. Following Wiener's terminology, this would mean that pieces of design can be incorporated into the white box, the model for the black box, which are identical to the true design of the latter. Thus, the white box may get blackish, or the black box whitish, the more borrowed knowledge is taken into consideration. The evolution of models in temperature regulation appears a suitable example to explicate—how the black-box approach and investigations providing borrowed knowledge may mutually complement each other in elucidating the function of a homeostatic system.

Studies during the past two decades have shown that thermosensory input functions in mammals are localized not only in the skin, hypothalamus, and spinal cord, but also in the lower brain stem and in deep body tissues outside of the central nervous system ([19], for references). The introduction of whole-body cooling in conscious experimental animals by Jessen et al. [10] and the corresponding data derived indirectly from other studies give a quantitative estimate for the contribution of all extrahypothalamic thermosensors, relative to the known thermosensors. For mammals, the magnitude of the metabolic cold defense or evaporative heat defense response (the output) to a given change of whole-body temperature (the input) was found to be, in general, severalfold greater than the corresponding responses produced by the same temperature changes of the hypothalamus, spinal cord, or skin [11]. In birds, the difference was even more striking, because the input-output relationships between changes of whole-body temperature and thermoregulatory effector activities corresponded to those in mammals, while the contributions of the hypothalamus were generally negligible. Figure 1 indicates the range of sensitivities for the metabolic cold defense effector to changes of hypothalamic temperature, in comparison to the range of sensitivities to changes of body temperature, as determined in several mammalian and avian species. As one piece of borrowed knowledge, we may deduce from these data the significance of central extrahypothalamic thermosensory inputs.

Another piece of borrowed knowledge which may be used in the construction of black-box models of thermoregulation is the existence of cold and warm receptors. In devising steady-state models of the active system, their inputs may be represented by the known static response curves of thermoreceptors. These curves have been evaluated very thoroughly for skin thermoreceptors and, although less thoroughly, for those ascending anterolateral tract neurons of the spinal cord which carry the signals from intraspinal thermoreceptive structures. As pointed out in 1973 by Hensel [12], the response characteristics of cutaneous cold and warm receptors are closely similar to those of the spinal cold and warm afferents, which are tentatively considered here as representative of central nervous thermoreceptors in general. As schematically demonstrated by Fig. 2, the characteristics of the static response curves of cold and warm detectors would be quite accurately modelled by adapting fifth-order polynomial expressions. However, these equations are not very handy. When modelling is
FIG. 1. The increase in metabolic heat production per 1°C decrease in whole-body temperature or hypothalamic temperature (ordinate) of various mammalian and avian species plotted against body weight (abscissa). **Whole-body temperature:** The upper hatched area encompasses 16 observations on ten mammalian and five observations on four avian species. One observation in man (open triangle) and one observation in the goose (solid triangle) outside of the indicated range are marked by open squares. **Hypothalamic temperature:** the lower shaded area encompasses 27 observations on 22 mammalian species. One observation in *Citellus lateralis* and one in the goat (open circles) outside of the indicated range are marked by open squares. All measurements in seven bird species (solid circles) are below the range of mammalian hypothalamic sensitivity, indicating the generally negligible thermosensory contribution of the hypothalamus in the avian class.

restricted to the range to which experimental body temperature changes—except those of the skin—are usually limited, replacing the polynomial by an exponential or linear approximation will result in terms for the cold and warm response curves sufficiently accurate to serve as input terms in a black box. The cold and warm signal inputs are subsequently described by linear terms, however, only for reasons of convenience.

In pictorial models of temperature regulation, the existence of cold and warm receptors has usually been accounted for in combination with another piece of borrowed knowledge: the Sherringtonian principles of neuronal interaction. Their significance in the central control of body temperature is supported by neurophysiological and neuropharmacological data [13]. By mutual inhibitory interconnections, the cold receptor inputs are assumed to stimulate cold defense and inhibit heat defense, whereas the warm receptor inputs would exert the opposite effects. However, the impossibility of accounting adequately for all inputs and outputs in a black-box model of temperature regulation forces us to present this knowledge in an approximately homomorphic way. Thus, just a few receptive input channels have usually been depicted in a symmetrical fashion, although there is a multitude of cold and warm receptors at many places with unknown quantitative relationships. Furthermore, the presentation of mutual inhibitory connections and input-output coupling has mostly been restricted to the hypothalamic level, although such interconnections are likely to
exist at various levels in the afferent and efferent pathways, and input-output coupling may occur at different levels of the central nervous axis [14].

The borrowed knowledge discussed, so far, is summarized in a steady-state model describing metabolic heat production $M$ as a function of body temperature $T_b$ by the following equation

$$M = M_O + C_{bm} \cdot (T_{co} - T_b) - W_{bm} \cdot (T_b - T_{wo})$$

[1]

Subtractive interaction of the warm and cold signal inputs is assumed according to the Sherringtonian principle. In the case of control of heat dissipation, the signs would be reversed. The cold and warm signal inputs are expressed by linear terms: i.e., in the simplest possible way. The terms $T_{wo}$ and $T_{co}$ indicate the temperatures at which the warm and cold receptor inputs become zero and, thus, do not represent set values. The relative weights of the cold and warm signal inputs in controlling metabolic cold defense are represented by the coefficients $C_{bm}$ and $W_{bm}$. The numerical values of these coefficients and of the constant $M_O$ are empirically determined by approximation of the equation to the experimentally determined relationship between $M$ and $T_b$. The equation is linear, in accordance with the results of whole-body cooling [9,11] and with the well-established proportional control property of the biological thermostat when working at steady-state conditions [15]. The model further implies that the signals of all cold sensors and of all warm sensors, respectively, interact additively to form the cold and warm signal inputs from the whole body.

The condition described by the above model is experimentally approached with the heat exchanger techniques, though never perfectly, so that some degree of variability in the match of the experimental data with the model has to be expected. If, on the other
hand, the heat exchanger technique is combined with the selective thermal stimulation of a certain thermosensory area, the contribution of this area has to be considered separately. This consideration would apply, for instance, to the combination of selective manipulations of hypothalamic temperature $T_{hy}$ with those of extrahypothalamic body temperature $T_{ex}$. Presuming basically identical thermal characteristics of hypothalamic and extrahypothalamic cold sensors and warm sensors, respectively, the steady-state conditions of $M$ as a function of $T_{ex}$ and $T_{hy}$ could be described by the following equation:

$$M = M_0 + \left[ C_{exm} \cdot (T_{co} - T_{ex}) + C_{hym} \cdot (T_{co} - T_{hy}) \right]$$

$$- \left[ W_{exm} \cdot (T_{ex} - T_{wo}) + W_{hym} \cdot (T_{hy} - T_{wo}) \right]$$

[2]

The relative weights of the extrahypothalamic and hypothalamic cold and warm signal inputs are expressed by the corresponding coefficients. This model differs from the classical additive model of hypothalamic temperature regulation in that warm and cold signal inputs are separately considered, with $T_{ex}$ comprising skin and extrahypothalamic deep-body temperature.

Another piece of borrowed knowledge which has emerged from the studies on hypothalamic thermoresponsive neurons but reflects a general thermodynamic property, is the $Q_{10}$ of signal transmission in the network of the hypothalamic thermostat [15]. This aspect was originally considered by Hammel [16] with the implication that, with a $Q_{10}$ of $>1$ for cold signal transmission and of $>1$ for warm signal transmission, there was no necessity to assume thermoreceptors to exist in the hypothalamus of mammals in order to explain its apparent thermosensory function. In the second class of homeotherms, the birds, the $Q_{10}$ temperature dependence of intrahypothalamic temperature signal transmission has received a more general significance by the disclosure of "non-sensory" effects of hypothalamic thermal stimulation on the thermoregulation of several species. These paradoxical effects were tentatively explained by assuming, for birds too, a general temperature dependence of intrahypothalamic temperature signal transmission with a $Q_{10} >1$, with, however, a greater $Q_{10}$ for cold than for warm signal transmission [17].

The presumption that central temperature signal transmission exhibits, in general, a $Q_{10} >1$ requires substantiation, as a piece of borrowed knowledge, by neurophysiological data. At the single-unit level this property should express itself in the way shown by the schematic diagram of Fig. 3. The relationship between temperature and discharge rate should be exponential and the slope in terms of impulses/second/°C should depend on both the $Q_{10}$ and the control discharge rate. At a given $Q_{10}$, this would mean that the sensitivity in terms of impulses/second/°C should be proportional to the control discharge rate. For hypothalamic single units, studies on conscious ducks have, indeed, demonstrated that their local thermoresponsiveness was closely similar to what had to be theoretically expected for the $Q_{10}$ type of temperature dependence [18]. Moreover, the majority of the investigated units were shown to receive synaptic inputs and thus fulfilled the precondition necessary to explain their thermoresponsiveness by temperature dependence of synaptic transmission.

If the borrowed knowledge of a $Q_{10} >1$ is to be incorporated into a model of thermoregulation, this could be done by introducing as a coefficient the exponential term:

$$[U^{(T_{wo} - T_o)}]$$

[3]
in which \( U \) is chosen so that with \( (T_{\text{nO}} - T_s) = -10 \) the term would assume a value corresponding to the presumed Q_{10} value. Again, \( T_{\text{nO}} \) is not a set value but indicates an arbitrary "network" temperature for 1:1 synaptic signal transmission.

For the metabolic cold response to a change of whole-body temperature, the consideration of this term would lead to the following model:

\[
M = M_0 + [C_{bm} \cdot (T_{c0} - T_b)] \cdot [U_c(t_{\text{wO}} - T_b)] - [W_{bm} \cdot (T_b - T_{\text{wO}})] \cdot [U_w(t_{\text{wO}} - T_b)]
\]  

\[4\]
The "network" temperature is assumed to be identical with whole-body temperature. \( U_c \) and \( U_w \) may be different but generally \(<1\), corresponding to an overall Q_{10} > 1. The exponential terms would predict that the relationship between metabolic heat production and body temperature should not be rectilinear. However, considering that the maximum capacity of the cold defense effector was found to be attained with a 2–3°C decrease of body temperature, it is not surprising that substantial deviations from a rectilinear relationship have not been observed, as a rule [11]. However, if sites of synaptic transmission of cold or warm signal inputs within the central nervous system (brain stem, spinal cord) would be subjected to greater temperature variations, this non-linearity should become apparent.

In elucidating the proposed Q_{10} temperature dependence of temperature signal transmission by more pronounced temperature variations in thermo-integrative sections of the central nervous system, thermal stimulation of the hypothalamus was considered as a means to provide experimental evidence, irrespective of the significance attributed to the hypothalamus as a source of thermosensory inputs. Combining, for instance, independent manipulations of hypothalamic temperature and of extrahypothalamic body temperature in evaluating metabolic cold defense should be matched by the following equation:

\[
M = M_0 + \left[ C_{\text{exm}} \cdot (T_{c0} - T_{ex}) + C_{\text{hym}} \cdot (T_{c0} - T_{hy}) \right] \cdot [U_c^{(T_{e0} - T_e)}]
- \left[ W_{\text{exm}} \cdot (T_{ex} - T_{w0}) + W_{\text{hym}} \cdot (T_{hy} - T_{w0}) \right] \cdot [U_w^{(T_{wo} - T_w)}] \tag{5}
\]

The model assumes that intra- and extrahypothalamic cold inputs are subject to the same temperature dependence of intrahypothalamic transmission, as are the intra- and extrahypothalamic warm inputs. To account for the proposal that, in case of a Q_{10} \geq 1 for extrahypothalamic warm signal transmission and a Q_{10} > 1 for cold signal transmission, the assumption of hypothalamic thermoreceptors is not necessary [16], the coefficients \( C_{\text{hym}} \) and \( W_{\text{hym}} \) may be set at zero.

The test experiments consisted in the evaluation of \( M \) as a function of \( T_{ex} \) in rabbits by means of an intestinal cooling thermode at two levels of \( T_{hy} \) established by means of a chronically implanted hypothalamic thermode [19]. The main result of the numerical adaptation to be mentioned here was that equation 5 could be matched with the experimental data by attributing a Q_{10} of about 8.5 to warm signal transmission and a Q_{10} of about 1.5 to cold signal transmission [20]. This result would correspond to the hypothesis which explains the apparent thermosensory function of the mammalian hypothalamus by assuming that the Q_{10} of intrahypothalamic transmission of the extrahypothalamic warm signals is greater than that of the cold signals [16].

The comparison of equation 5 as a model of mammalian thermoregulation with the classical additive [7,15] and multiplicative [21,22] models of hypothalamic thermoregulation would reveal similarities as well as dissimilarities with regard to the interrelationships between hypothalamic and extrahypothalamic temperatures and the effector activities controlled by these inputs. One difference our model predicts is that the relationship between \( T_{hy} \) and effector activity should not be rectilinear, if the Q_{10} component of hypothalamic thermoresponsiveness becomes relevant. This prediction could, indeed, be confirmed in studies on thermal panting as a function of \( T_{hy} \) in rabbits [23]. Another difference concerns the sensitivity of effector responses to a given change in extrahypothalamic or hypothalamic temperature. The additive model proposes that these sensitivities are independent of \( T_{hy} \). The multiplicative model proposes that the sensitivities to hypothalamic and extrahypothalamic temperature
changes are inversely related to each other, with the former decreasing and the latter increasing with decreasing $T_{h_y}$ or with increasing skin temperature, respectively. Equation 5, which takes into account that central temperature signal transmission is generally temperature-dependent with a $Q_{10} > 1$, would propose an inverse relationship between $T_{h_y}$ and the sensitivities to both hypothalamic and extrahypothalamic thermal stimuli, regardless of whether the greater $Q_{10}$ is attributed to the cold or the warm signal pathway. It would, therefore, apply equally to mammals and birds. The decrease in sensitivity with decreasing $T_{h_y}$ has, in fact, been observed in a mammal, the rabbit, and in a bird, the duck, for both metabolic cold defense and respiratory heat defense, although both species differed fundamentally with respect to the influence of hypothalamic cooling on the thresholds of effector activation [24].

The classical additive and multiplicative models of mammalian thermoregulation have proceeded from an at least apparent thermosensory function of the hypothalamus and, thus, cannot be reconciled with the generally weak and partially inappropriate effects of hypothalamic thermal stimulation on temperature regulation in birds ([25], for references). When the thermoreceptive function of the hypothalamus is conceptually separated from the $Q_{10}$-type temperature dependence of intrahypothalamic temperature signal transmission, the paradoxical effects of hypothalamic thermal stimulation in birds can be accounted for, as proposed above, by attributing a $Q_{10}$ to the cold signal pathway greater than the $Q_{10}$ of the warm signal pathway. When a $Q_{10}$ of about 3.5 for the former and one of about 2.5 for the latter pathway were tentatively assumed, the above model (equation 5) could be matched with the results of studies on ducks in which metabolic heat production and thermal panting were investigated as functions of $T_{h_y}$ and $T_{ex}$ in the same manner as in the experiments on rabbits [26]. The lacking or negligible thermosensory function of the avian hypothalamus in the normothermic range was accounted for by presuming small or no contribution of hypothalamic cold sensors to the thermosensory inputs in birds. Considering further that certain sensors may be differently connected to different thermoregulatory effectors [14], even complex combinations of partially adequate and partially inadequate relationships between $T_{h_y}$ and various effector responses in the same bird could be described by the same basic equation [25].

The presumed piece of borrowed knowledge, namely, of greater $Q_{10}$ for cold than for warm signal transmission, could be substantiated by neurophysiological evidence [27]. Locally thermoresponsive units in the hypothalamus of conscious ducks with a $Q_{10} > 1$ were classified according to whether they were depressed or activated by extrahypothalamic cooling. The statistical comparison of two samples of warm and cold reactive units showed that, indeed, the local $Q_{10}$ values of the latter were significantly greater, on the order of 4 on average, as compared to the average $Q_{10}$ of 2 for the former.

In a study on rabbits, $T_{ex}$ was clamped, in a warm environment, at three different levels and panting rate was determined as a function of $T_{h_y}$ [23]. The model of equation 5 was shown to match the experimental data by assuming a $Q_{10}$ of about 8.5 for warm signal transmission and of about 1.5 for cold signal transmission and no hypothalamic thermoreceptors. The data could be matched equally well by assuming a $Q_{10}$ of about 3.5 for cold and of about 2.5 for warm signal transmission and additional hypothalamic cold and warm receptors. In other words, the $Q_{10}$ distribution proposed for birds appeared theoretically applicable to mammals, too, in describing the influence of $T_{h_y}$ on thermal panting. Metabolic cold defense of the rabbit as a function of $T_{h_y}$ and of body temperature could also be described in either way [20].
In conclusion, the analysis of the active system of homeothermic temperature regulation by combining the black-box approach with the systematic acquisition and incorporation of borrowed knowledge presently offers the alternative of two opposing $Q_{10}$ distributions underlying equivalent models with regard to mammalian temperature regulation, whereas only one type of $Q_{10}$ distribution appears applicable to avian temperature regulation. In this situation additional borrowed knowledge is required to decide whether birds and mammals agree in their $Q_{10}$ distribution but differ in the density of primary thermosensors at the hypothalamic level, or whether they differ in either respect. The questions to be answered are, first, is there evidence for thermosensitive neurons with thermoreceptive functions in the mammalian hypothalamus, and, second, is there evidence for “inappropriate” effects of $T_k$ on thermoregulation in mammals [28] similar to those seen in birds. Pieces of circumstantial evidence suggest as working hypotheses that the answer to each question might be “yes.” These hypotheses may be taken as concluding examples for the usefulness of the black-box concept when it not only accepts but rather aims at the acquisition and systematic incorporation of borrowed knowledge. This approach may be seen as the attempt to hybridize the black box, the system that we investigate, with the white box, the system that we are devising as a model. Its further pursuit may help to consider in future models those properties of the biological thermostat which modify the functions of the basic negative feedback circuits of temperature control—for instance, input gating and multilevel control of input signal processing as well as of input-output coupling [29].

1See Boulant JA: Single neuron studies and their usefulness in understanding thermoregulation. Yale J Biol Med 59:179–188, 1986.

REFERENCES

1. Grodins FS: Theories and models in regulatory biology. In Physiological and Behavioral Temperature Regulation. Edited by JD Hardy, AP Gagge, JAJ Stolwijk. Springfield, IL, Thomas, 1970, pp 722–726
2. Hardy JD, Gagge AP, Stolwijk JAJ: Physiological and Behavioral Temperature Regulation. Springfield, IL, Thomas, 1970, 944 pp
3. Bligh J, Moore R: Essays on Temperature Regulation. Amsterdam, North-Holland, 1972, 186 pp
4. Wiener N: Cybernetics, 2nd edition, 1961. First German edition, Duesseldorf, Econ, 1963, 287 pp
5. Ashby WR: An Introduction to Cybernetics. In The Black Box. London, Methuen, 1956, pp 86–117
6. Stolwijk JAJ: Mathematical model of thermoregulation. In Physiological and Behavioral Temperature Regulation. Edited by JD Hardy, AP Gagge, JAJ Stolwijk. Springfield, IL, Thomas, 1970, pp 703–721
7. Hammel HT, Jackson DC, Stolwijk JAJ, Hardy JD, Strömme S: Temperature regulation by hypothalamic proportional control with an adjustable setpoint. J Appl Physiol 18:1146–1154, 1963
8. Stitt JT, Hardy JD, Stolwijk JAJ: PGE, fever: its effect on thermoregulation at different low ambient temperatures. Am J Physiol 227:662–629, 1974
9. Jessen C, Feistkorn G: Some characteristics of core temperature signals in the conscious goat. Am J Physiol 247:R456–R464, 1983
10. Jessen C, Mercer JB, Puschmann S: Intravascular heat exchanger for conscious goats. Pfluegers Arch 368:263–265, 1977
11. Mercer JB, Simon E: A comparison between total body thermosensitivity and local thermosensitivity in mammals and birds. Pfluegers Arch 400:228–234, 1984
12. Hensel H: Neural processes in thermoregulation. Physiol Rev 53:948–1017, 1973
13. Bligh J: Temperature regulation: a theoretical consideration incorporating Sherringtonian principles of central neurology. J Therm Biol 9:3–6, 1984
14. Simon E: Temperature regulation: the spinal cord as a site of extrahypothalamic thermoregulatory functions. Rev Physiol Biochem Pharmacol 74:641–710, 1974
15. Hammel HT: Regulation of internal body temperature. Ann Rev Physiol 30:641–710, 1968
16. Hammel HT: Neurons and temperature regulation. In Physiological Controls and Regulations. Edited by WS Yamamoto, JR Brobeck. Philadelphia, Saunders, 1965, pp 71–97
17. Simon-Oppermann C, Simon E: Cold defence activity of Pekin ducks during general hypothermia in comparison to heat defence during hyperthermia: effect of POAH cooling on threshold and gain. In Contributions to Thermal Physiology. Edited by Z Szelenyi, M Szekely. Budapest, Akademiai Kiado, 1980, pp 89–91
18. Eissel K, Simon E: How are neuronal thermosensitivity and lack of thermoreception related in the duck’s hypothalamus? A tentative answer. J Therm Biol 5:219–223, 1980
19. Inomoto T, Mercer JB, Simon E: Opposing effects of hypothalamic cooling on threshold and sensitivity of metabolic response to body cooling in rabbits. J Physiol (London) 322:139–150, 1982
20. Simon E, Mercer JB, Inomoto T: Temperature-dependent synapses and primary thermosensors in the thermoregulatory central nervous network. J Therm Biol 8:137–139, 1983
21. Stitt J: The regulation of respiratory evaporative heat loss in the rabbit. J Physiol (London) 258:157–171, 1976
22. Stitt J: Variable open-loop gain in the control of thermogenesis in cold-exposed rabbits. J Appl Physiol 48:494–499, 1980
23. Inomoto T, Mercer JB, Simon E: Interaction between hypothalamic and extrahypothalamic body temperature in the control of panting in rabbits. Pfluegers Arch 398:142–146, 1983
24. Simon E: Extrahypothalamic thermal inputs to the hypothalamic thermoregulatory network. J Therm Biol 9:15–20, 1984
25. Schmidt I, Simon E: Negative and positive feedback of central nervous system temperature in thermoregulation of pigeons. Am J Physiol 243:R363–R372, 1982
26. Simon E: Effects of CNS temperature on generation and transmission of temperature signals in homeotherms: a common concept for mammalian and avian thermoregulation. Pfluegers Arch 392:79–88, 1981
27. Lin MT, Simon E: Properties of high Q lo units in the conscious duck's hypothalamus responsive to changes of core temperature. J Physiol (London) 322:127–137, 1982
28. Puschmann S, Jessen C: Anterior and posterior hypothalamus: effects of independent temperature displacements on heat production in conscious goats. Pfluegers Arch 373:59–68, 1978
29. Simon E, Pierau FK, Taylor DCM: Central and peripheral thermal control of effectors in homeothermic temperature regulation. Physiol Rev, in press