HIGHLIGHTED TOPIC | A Physiological Systems Approach to Human and Mammalian Thermoregulation

Neuronal basis of Hammel’s model for set-point thermoregulation

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Boulant, Jack A. Neuronal basis of Hammel’s model for set-point thermoregulation. J Appl Physiol 100: 1347–1354, 2006; doi:10.1152/japplphysiol.01064.2005.—In 1965, H. T. Hammel proposed a neuronal model to explain set-point thermoregulation. His model was based on a synaptic network encompassing four different types of hypothalamic neurons: i.e., warm-sensitive and temperature-insensitive neurons and heat loss and heat production effector neurons. Although some modifications to this model are suggested, recent electrophysiological and morphological studies support many of the model’s major tenets. Hypothalamic warm-sensitive neurons integrate core and peripheral thermal information. These neurons sense changes in hypothalamic temperature, and they orient their dendrites medially and laterally to receive ascending afferent input from cutaneous thermoreceptors. Temperature-insensitive neurons have a different dendritic orientation and may provide constant reference signals, which are important in determining thermoregulatory set points. In Hammel’s model, temperature-sensitive and -insensitive neurons send mutually antagonistic synaptic inputs to effector neurons controlling various thermoregulatory responses. The model predicts that warm-sensitive neurons synaptically excite heat loss effector neurons and inhibit heat production effector neurons. In recent studies, one counterpart of these effector neurons may be “excitatory postsynaptic potential-driven neurons,” the activity of which is dependent on synaptic excitation from nearby cells. Excitatory postsynaptic potential-driven neurons have sparse dendrites that appear to be specifically oriented, either medially or laterally, presumably to receive selective synaptic input from a discrete source. Another counterpart of effector neurons may be “silent neurons,” which have extensive dendritic branches that may receive synaptic excitation from remote sources. Because some silent neurons receive synaptic inhibition from nearby warm-sensitive neurons, Hammel’s model would predict that they have a role in heat production or heat retention responses.

hypothalamus; neuron; synaptic network; body temperature

IN 1965, H.T. HAMMEL (20) published “Neurons and Temperature Regulation” as a chapter in the book, Physiological Controls and Regulations. This classic paper described a model in which a simple synaptic network of hypothalamic neurons regulates body temperature around a set-point temperature (Tset). Most of the components of Hammel’s original model are shown in Fig. 1. Over the last 40 years since its publication, Hammel’s elegant neuronal model has served both thermal and neural physiologists. It has helped scientists to interpret their data and generate hypotheses. It has fostered a host of similar, more complex models, and it has contributed to an ongoing debate over the meaning of “set point.” The purpose of this paper is to present Hammel’s neuronal model and describe recent electrophysiological studies that either support the model or suggest its modification.

Early studies, including those of Hammel and coworkers, used thermode-implanted animals to warm and cool discrete parts of the rostral hypothalamus while measuring thermoregulatory responses (1, 21, 22, 28, 33). These studies identified the preoptic area and anterior hypothalamus (PO/AH) as an important thermosensitive region that could evoke both physiological and behavioral responses (reviewed in Refs. 3, 4). The right side of Fig. 1 plots the magnitude of heat loss and heat production responses during changes in PO/AH temperature. When the PO/AH is warmed above Tset, there are proportional increases in responses that promote heat loss. Depending on the animal, these heat loss responses could include panting, sweating, cutaneous vasodilation, and behaviors that facilitate peripheral cooling. Each of these responses has its own Tset, such that different responses are evoked at slightly different hypothalamic temperatures. The right side of Fig. 1 also shows that PO/AH cooling produces responses that promote either heat production or heat retention. These responses could include nonshivering thermogenesis (due to metabolic hormones or brown adipose tissue), shivering, cutaneous vasoconstriction, and behaviors that facilitate skin warming (e.g., huddling and seeking warm environments). Again, each response has its own Tset, and the
magnitude of that response is proportional to the hypothalamic cooling below $T_{\text{set}}$.

**WARM-SENSITIVE AND TEMPERATURE-INSENSITIVE NEURONS**

The neuronal network in Hammel’s model was inspired by the electrophysiological recordings of Hammel’s colleague, Teruo Nakayama, whose initial recordings found two types of preoptic neurons based on their action potential firing rate (FR) responses to thermode-induced changes in PO/AH temperature (34, 35). As illustrated in the bottom left of Fig. 1, the majority of neurons show little or no change in their FRs during hypothalamic warming and cooling. These temperature-insensitive neurons are labeled “I” in Fig. 1, but early studies also referred to them as temperature-unresponsive (34, 35) or low-$Q_{10}$ neurons (20). In contrast, Nakayama et al. (34, 35) found that $\sim20\%$ of the neurons strongly increased their FRs during increases in hypothalamic temperatures. These are classified as warm-sensitive neurons, labeled “W” in Fig. 1, and early studies referred to them as temperature-responsive or high-$Q_{10}$ neurons. Over the years, these same two types of neurons have been recorded both in vivo and in vitro throughout the hypothalamus in a variety of species, and the proportions have remained remarkably consistent; i.e., usually $>70\%$ are temperature insensitive and $>20\%$ are warm sensitive (reviewed in Refs. 4, 5).

Figure 2 shows the effect of temperature on intracellularly recorded action potentials in two types of preoptic neurons recorded in rat hypothalamic tissue slices (17). Both neuronal types display common features. The resting membrane potentials of both neurons respond similarly to temperature changes. Therefore, thermal effects on resting membrane potential do not appear to be the primary determinants of neuronal thermosensitivity (16, 42). As shown in Fig. 2, each action potential is followed by a fast after-hyperpolarizing potential and then a slow depolarizing prepotential (or pacemaker potential), leading to threshold and the generation of the next action potential.
Temperature has little or no effect on the depolarizing prepotentials of the temperature-insensitive neurons, and the interspike interval between their action potentials remains fairly constant. On the other hand, in warm-sensitive neurons, increasing temperature causes an increase in the prepotential’s rate of depolarization. One study (17) suggests that much of this prepotential thermosensitivity is due to the inactivation of the A-type potassium current ($I_A$), a transient outward hyperpolarizing $K^+$ current. Immediately after each action potential and after-hyperpolarizing potential, $I_A$ activates and briefly holds the membrane at a hyperpolarized level. Following this, however, $I_A$ inactivates, which allows the neuron to depolarize toward the next action potential. Warming strongly increases the rate of $I_A$ inactivation, and this causes the prepotential to depolarize at a faster rate. Thus threshold is reached faster, the interspike interval is shortened, and FR is increased. Accordingly, the cellular mechanism for neuronal warm sensitivity lies in the thermosensitive elements of the depolarizing prepotential. The combination of brief ionic currents responsible for the prepotential underlies the mechanistic distinctions between neuronal temperature sensitivity and insensitivity (17).

Both types of neurons also receive synaptic inputs from nearby neurons. Intracellular recordings usually display inhibitory postsynaptic potentials (IPSPs) and to a lesser degree, excitatory postsynaptic potentials (EPSPs) (18). As an example, prominent IPSPs can be seen at each temperature in the three records of the warm-sensitive neuron in Fig. 2. This inhibitory synaptic input often comes from nearby temperature-insensitive neurons, since the frequency of IPSPs is usually not affected by temperature. Some studies have shown that temperature can alter the effectiveness of postsynaptic potentials, such that IPSPs (even those originating presynaptically from a temperature-insensitive neuron) can enhance the thermosensitivity of a warm-sensitive neuron (9, 11). In most cases, however, this local synaptic activity makes only a minor contribution to a neuron’s thermosensitivity. Tissue slice studies using perfusion media that block all synaptic activity report relatively normal proportions of preoptic warm-sensitive and temperature-insensitive neurons (12, 30, 32). Aside from the local synaptic inputs on warm-sensitive and temperature-insensitive neurons, electrophysiological studies tend to substantiate the basic elements of Hammel’s model. Most spontaneously firing PO/AH neurons can be grouped into two populations: one is relatively insensitive to temperature, and the other smaller population is intrinsically warm sensitive.

The basis of Hammel’s model lies in the synaptic network that the warm-sensitive and temperature-insensitive neurons form with effector neurons controlling specific thermoregulatory responses. Some of these effector neurons may be located nearby, within the PO/AH itself. Other effector neurons may be located in different hypothalamic areas, such as the posterior hypothalamus (23, 36). Still other effector neurons may be located more caudally in the brain stem, e.g., in the midbrain periaqueductal gray and ventral tegmental area (31, 39–41). Figure 1 shows two different effector neurons. One neuron controls a heat loss response and is labeled with a small “c” because (synaptically) it has cold-sensitive characteristics; i.e., its FR increases during cooling.

HEAT LOSS EFFECTOR NEURONS

Hammel’s model suggests that the heat loss effector neurons are either spontaneously firing neurons or silent neurons that are synaptically excited by warm-sensitive neurons and synaptically inhibited by temperature-insensitive neurons. In Fig. 1 (top center), the two dotted lines in the graph near the heat loss effector neuron represent these two antagonistic synaptic inputs, where the frequency of (+) EPSPs has the same thermal profile as the warm-sensitive neuron and the frequency of (−) IPSPs has the same thermal profile as the temperature-insensitive neuron. Note that the two dotted lines cross at a temperature near 37°C, suggesting that these two opposing synaptic events negate each other at this temperature. Admittedly, an IPSP is not the exact opposite of an EPSP; i.e., magnitude and timing of these postsynaptic potentials determine their effectiveness in producing or suppressing action potentials. Nevertheless, the concept of Hammel’s model is that the summation of these two antagonistic synapses ultimately determines the FR of the effector neuron. The solid line in this graph shows the postsynaptic neuron’s FR based solely on the two antagonistic inputs. At some temperature (possibly near 37°C), the amount of effective synaptic inhibition (IPSP frequency) balances the amount of synaptic excitation (EPSP frequency). If the effector neuron’s activity is determined only by these two synaptic inputs, the neuron’s FR should be at a low or minimal level. Furthermore, at all cooler temperatures, the effector neuron’s FR should remain at this minimal level, since the inhibitory synaptic activity is always greater than the excitatory synaptic activity. On the other hand, when the temperature increases above 37°C, EPSP frequency will increase, but IPSP frequency will remain constant. This is because synaptic excitation is coming from a warm-sensitive neuron, whereas synaptic inhibition is coming from a temperature-insensitive neuron. Based on these two synaptic inputs, the FR of the heat loss effector neuron should increase proportionally as hypothalamic temperature rises above 37°C. Therefore, an effector neuron’s $T_{set}$ is the temperature at which there is an effective balance between excitatory and inhibitory inputs. When hypothalamic temperature exceeds $T_{set}$, there is a proportional increase in the neuron’s FR, causing a proportional increase in a heat loss response. This increased heat loss will eventually reduce body temperature and hypothalamic temperature, which is the feedback signal “sensed” by the warm-sensitive neurons.

In this way, Hammel has functionally identified the neural components of a negative feedback control system. In the “black box” diagrams of most thermoregulatory control systems, an “error-comparator” compares a feedback signal (i.e., body temperature) with a reference signal that represents set point. If the feedback signal differs from the reference signal, the error-comparator generates a correcting output that evokes a thermoregulatory response (either heat loss or heat production) to return body temperature back toward the $T_{set}$. In Hammel’s model, the reference signal is the constant, unchanging FR of the temperature-insensitive neuron. The error-comparator is the antagonistic excitatory and inhibitory inputs from the warm-sensitive and temperature-insensitive neurons synapsing on the effector neuron, and set point is the temperature at which synaptic inhibition balances with synaptic excitation.

Some electrophysiological studies lend support to Hammel’s concept of a set-point effector neuron. Early extracellular
Intracellular recordings also provide the ability to count the frequencies of EPSPs and IPSPs. As shown in Fig. 3, for example, by applying a slight hyperpolarizing current, action potentials can be briefly suppressed so that EPSPs and IPSPs can be counted. Alternatively, the same neuron could be voltage clamped, which eliminates action potentials and allows excitatory and inhibitory postsynaptic currents to be counted (9). Both types of analysis show that most hypothalamic neurons receive excitatory and inhibitory synaptic input from nearby neurons, but usually the inhibitory inputs are predominant (18). Even EPSP-driven neurons tend to have more IPSPs than EPSPs. Figure 4 shows the effect of temperature on the frequency of IPSPs and EPSPs in different EPSP-driven neurons recorded in PO/AH tissue slices. Each plot in Fig. 4 is from a single EPSP-driven neuron, showing the IPSP or EPSP frequencies at three different hypothalamic temperatures. As noted, with a few exceptions, temperature has little effect on the IPSP frequencies. This indicates that most of the neurons received synaptic inhibition from nearby temperature-insensitive neurons. On the other hand, for most of the neurons in Fig. 4, warming increased the frequencies of EPSPs, suggesting that they received synaptic excitation from nearby warm-sensitive neurons. EPSP-driven neurons are the only PO/AH population to show a significant increase in EPSP frequencies during warming (18). This synaptic network would be similar to that of the heat loss effector neurons in Hammel’s model; i.e., neurons that are excited by warm-sensitive neurons and inhibited by temperature-insensitive neurons.

**HEAT PRODUCTION EFFECTOR NEURONS**

The remaining effector neuron in Hammel’s model (Fig. 1, bottom center) controls heat production (and heat retention) responses that are usually initiated when the PO/AH is cooled below its normal temperature. This effector neuron would appear to be cold sensitive, showing an increased FR during hypothalamic cooling. Hammel predicted that these neurons are not intrinsically cold sensitive, but, instead, receive their cold sensitivity through synaptic inhibition from nearby warm-sensitive neurons. As shown in Fig. 1, the heat production effector neuron would also be an EPSP-driven neuron, since it

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**Fig. 3.** Action potentials and postsynaptic potentials recorded in a preoptic excitatory postsynaptic potential (EPSP)-driven neuron. Down arrows, EPSPs; up arrows, IPSPs. Top record shows that action potentials occur when EPSPs reach threshold. Bottom record shows that EPSPs and IPSPs can be counted when the action potentials are eliminated during a slight 12-pA hyperpolarizing current injection. [From Griffin et al. (18).]

**Fig. 4.** Effect of temperature on the frequency (postsynaptic potential/second) of IPSPs and EPSPs in different EPSP-driven neurons recorded in rat hypothalamic tissue slices. Each plot represents the frequency of IPSPs and EPSPs in individual preoptic area and anterior hypothalamus neurons. Thermal response plots suggest that some EPSP-driven neurons receive synaptic inhibition from nearby temperature-insensitive neurons and synaptic excitation from probable warm-sensitive neurons. [From Griffin et al. (18).]
receives excitatory synaptic input from a temperature-insensitive neuron. The dotted lines show the thermal profiles of the effector neuron’s two antagonistic synaptic inputs, with temperature-insensitive neurons contributing the (+) EPSPs and warm-sensitive neurons contributing the (−) IPSPs. At some temperature (e.g., possibly near 37°C), the amount of effective synaptic inhibition (IPSP frequency) balances the amount of synaptic excitation (EPSP frequency), and the effector neuron’s FR (solid line) should be at a low or minimal level. Also, this FR should remain low at warmer temperatures, since there are always more IPSPs compared with EPSPs. On the other hand, as the temperature drops below 37°C, the frequency of IPSPs would decrease, whereas the frequency of EPSPs would remain constant. Therefore, the effector neuron’s FR will increase proportionally during further cooling.

Numerous in vivo and in vitro electrophysiological studies have recorded cold-sensitive neurons, although the proportion of PO/AH cold-sensitive neurons is usually very small (i.e., <10%) (5). Some tissue slice studies have characterized these cold-sensitive neurons before, during, and after perfusions with synaptic blockade media (containing high-magnesium and low-calcium concentrations). In the PO/AH, most of these neurons lose their cold sensitivity during synaptic blockade (12, 32). This supports Hammel’s model, which hypothesized that neuronal cold sensitivity is due to synaptic inhibition from nearby warm-sensitive neurons. Intracellular recordings of cold-sensitive neurons are rare; however, when these cells are recorded, they appear to be EPSP-driven neurons in which their cold sensitivity is synaptically derived (11). As an example, Fig. 5 shows an EPSP-driven PO/AH neuron that supports the predictions of Hammel’s model. The recorded cell appears to be inhibited by a warm-sensitive neuron, since the frequency of IPSPs decreases during hypothalamic cooling.

In addition to EPSP-driven neurons, cold-sensitive synaptic characteristics have been recorded intracellularly in another PO/AH neuronal population in hypothalamic tissue slices. These cells are classified as “silent neurons,” and they only fire action potentials when artificially excited by depolarizing current injections. Some silent neurons appear to receive synaptic inhibition from warm-sensitive neurons, since the frequency of their IPSPs increases during warming (18). In hypothalamic tissue slices, only local synaptic networks remain intact, and synaptic connections from remote locations and afferent fibers are cut. While silent neurons do not have spontaneous activity when recorded in tissue slices, it is likely that these neurons are highly dependent on synaptic inputs from distant locations. Accordingly, when recorded in vivo in intact animals, these silent neurons may be a type of EPSP-driven neuron that receives its synaptic input from either afferent pathways or remote neural sites.

**PERIPHERAL AFFERENT INPUT TO PO/AH NEURONS**

The final critical element of Hammel’s model is the afferent pathway of peripheral warm and cold receptors to the PO/AH neurons. In Hammel’s original model, it was proposed that PO/AH warm-sensitive neurons are excited by cutaneous warm receptor pathways, whereas PO/AH temperature-insensitive neurons are excited by cutaneous cold receptor pathways. Subsequent in vivo electrophysiological studies suggested a modification of this scheme, since PO/AH temperature-insensitive neurons receive little or no input from peripheral thermoreceptor pathways. On the other hand, the majority of PO/AH warm-sensitive and cold-sensitive neurons do receive synaptic input from ascending pathways, conveying thermoreceptive information from either the skin or other sites throughout the body, such as the spinal cord (6, 19, 26). Moreover, the neuronal responses to peripheral temperatures usually coincide with the responses to hypothalamic temperature; i.e., PO/AH warm-sensitive neurons are usually excited by increases in peripheral temperature and inhibited by decreases in peripheral temperature.

As suggested in Fig. 1, it appears that information from peripheral warm receptors and cold receptors is combined at lower neural levels, such as converging synaptic inputs upon spinal neurons in the dorsal horn (27). This combined afferent information ascends through the spinal cord and brain stem over multisynaptic somatosensory pathways to eventually synapse on PO/AH thermosensitive neurons (4). Earlier studies suggested that this cutaneous information ascends over spinothalamic and spinobulbar pathways, reaching the PO/AH through synaptic relays in the reticular formation (3, 29). In the hypothalamus, afferent signals ascend in medial and lateral
of these insensitive neurons is to provide a constant, unchanging thermal information. In Hammel’s model, the importance away from the medial and lateral pathways, conveying peripheral input is also suggested by their morphology, since their dendrites or spinal temperatures. This lack of thermal afferent responds to hypothalamic temperature, nor do they respond to laterally to collect and compare peripheral thermoreceptor temperature, but they also send their dendrites medially and sense changes in their own temperature (which is core body and peripheral thermal information. Not only do these neurons supports the idea that these neurons serve to integrate central and peripheral thermal information. Not only do these neurons have extensive dendrites, oriented in all directions. [From Griffin et al. (18).]

Invited Review

**BASIS OF HAMMEL’S NEURONAL MODEL**

![Fig. 6. Representative morphology of four different neuronal types recorded in horizontal tissue slices of rat hypothalamus. Third ventricle represents the midline, and the rostral direction is at the top. Generally, dendrites of temperature-insensitive neurons have rostral-caudal and dorsal-ventral orientations, and warm-sensitive neurons have medial-lateral orientations. EPSP-driven neurons have sparse dendrites oriented either laterally or medially. Silent neurons have extensive dendrites, oriented in all directions. [From Griffin et al. (18).] Fiber pathways (38). Recent studies also indicate that peripheral thermoreceptor information can ascend more directly from the spinal cord in a spinohypothalamic tract (10, 18, 37). This pathways projects bilaterally through the hypothalamus, both medially in periventricular fibers and laterally in the medial forebrain bundle.]

**MORPHOLOGY OF DIFFERENT TYPES OF PO/AH NEURONS**

Figure 6 shows the morphological characteristics of four different types of PO/AH neurons. These four morphologically distinct cell types generally coincide with the four types of neurons in Hammel’s model. Warm-sensitive neurons have dendritic branches that extend both medially toward the midline periventricular fibers and laterally toward the medial forebrain bundle in the lateral hypothalamus. Because these warm-sensitive neurons also receive peripheral thermoreceptive afferent input, this medial-lateral dendritic orientation supports the idea that these neurons serve to integrate central and peripheral thermal information. Not only do these neurons sense changes in their own temperature (which is core body temperature), but they also send their dendrites medially and laterally to collect and compare peripheral thermoreceptor information ascending over two different afferent pathways.

In contrast, PO/AH temperature-insensitive neurons do not respond to hypothalamic temperature, nor do they respond to skin or spinal temperatures. This lack of thermal afferent input is also suggested by their morphology, since their dendrites are oriented parallel to the midline third ventricle and away from the medial and lateral pathways, conveying peripheral thermal information. In Hammel’s model, the importance of these insensitive neurons is to provide a constant, unchanging reference signal to the heat loss and heat production effector neurons. Because of the antagonistic synaptic inputs, the thermosensitive signal from the warm-sensitive neurons is compared with the reference signal from the temperature-insensitive neurons. Hammel’s model suggests that this synaptic comparison determines the $T_{set}$ for all thermoregulatory responses.

When Hammel’s neuronal model was published, it offered some unique concepts that were not present in other feedback control models. Other more complex models made clear distinctions between neurons that acted as “sensors,” compared with neurons that acted as “integrators.” Usually, in the other models, core temperature was sensed by hypothalamic warm or cold sensors, and this information was conveyed synaptically to an “interneuron,” which also received ascending afferent signals from peripheral thermal receptors (2, 24). It was the interneuron (not the warm-sensitive neuron) that integrated incoming signals from central and peripheral thermoreceptors. Hammel’s model, however, suggested that the same hypothalamic neuron could act as both a “sensor” and an “integrator.” This concept is supported by electrophysiological studies, suggesting that PO/AH warm-sensitive neurons are cells that sense many properties of the internal and external environments. Their depolarizing prepotentials allow them to change their FRs in response to changes in the internal temperature and possibly other endogenous factors (e.g., osmolality, glucose, hormones, etc.) (7, 8). In addition, the medial-lateral orientation of their dendritic branches allows them to receive and compare synaptic inputs arriving over different afferent pathways. This is not to say that interneurons or thermoregulatory effector neurons cannot also serve an integrative role. A good example may be the previously mentioned PO/AH silent neurons, the activity of which may be highly dependent on afferent input from peripheral thermoreceptive pathways, but, at the same time, some of these silent neurons are synaptically inhibited and controlled by nearby warm-sensitive neurons.

Another unique feature of Hammel’s studies was the concept of an “adjustable” $T_{set}$, where the regulated $T_{set}$ could be “shifted” to higher or lower temperatures by a variety of internal and external conditions known to affect thermoregulation (20, 22). Internal conditions include endogenous factors (e.g., pyrogens, reproductive hormones, osmolality), and external conditions include synaptic inputs from peripheral warm and cold receptors or from joint receptors activated during exercise. Regardless of the internal or external condition, Hammel hypothesized that it could increase or decrease the regulated $T_{set}$. Furthermore, he used his neuronal model to explain how the PO/AH accomplished the shift in set point. Figure 1 shows that $T_{set}$ for both heat loss and heat production effector neurons is the temperature at which there is a balance between antagonistic synaptic inputs from PO/AH warm-sensitive and temperature-insensitive neurons. Therefore, a shift in $T_{set}$ could occur simply by changing the FR of either neuronal type. For example, if a pyrogen causes fever by elevating the $T_{set}$, this could occur by either decreasing the FRs of warm-sensitive neurons or increasing the FRs of temperature-insensitive neurons. Either or both of these neuronal responses would elevate the temperature at which there is a balance of excitatory and inhibitory synaptic inputs to the thermoregulatory effector neurons. This type of mechanistic explanation has been one of the most valuable aspects of Hammel’s model, for
it allows investigators to predict and explain how a host of conditions might affect thermoregulatory neurons and their efferent responses.

NEURONAL CORRELATES IN HAMMEL’S SYNAPTIC NETWORK

Electrophysiological studies show that the temperature-insensitive neuron is the predominant neuronal type in PO/AH synaptic networks. Not only are the majority of neurons temperature insensitive, but also most of the local synaptic activity appears to come from temperature-insensitive neurons. IPSPs and EPSPs are observed in most PO/AH intracellular recordings; however, as illustrated in Fig. 4, temperature usually has little effect on the frequencies of these postsynaptic potentials. This suggests that the majority of synapses present in local PO/AH networks are formed by populations of temperature-insensitive neurons.

As Fig. 6 suggests, EPSP-driven neurons have morphologies that are different from warm-sensitive and temperature-insensitive neurons. An EPSP-driven neuron is a neuron the FR of which is primarily due to excitatory synaptic input from other neurons. Hammel’s model (Fig. 1) shows the synaptic networks for heat loss effector neurons and heat production effector neurons. Both of these effector neurons could be considered to be “EPSP-driven,” since their FRs are effectively due to excitatory synaptic inputs from either warm-sensitive or temperature-insensitive neurons. Figure 6 shows the typical morphology of a hypothalamic EPSP-driven neuron (18). Compared with other neurons, EPSP-driven neurons have sparse dendritic trees, which tend to be oriented either medially or laterally, but (unlike warm-sensitive neurons) not in both directions. EPSP-driven neurons appear to receive their synaptic inputs more selectively, either from medial inputs or from lateral inputs. This may support Hammel’s model and a series of experiments by Kanosue and coworkers (31, 40), suggesting that there are discrete populations of thermosensitive and efferent neurons controlling each thermoregulatory response. Each group of efferent neurons may be dependent on antagonistic synaptic inputs from separate populations of warm-sensitive and temperature-insensitive neurons.

Although not suggested in Hammel’s model, the distinct medial or lateral dendritic orientations of the EPSP-driven neurons raise the possibility that these neurons could receive specific peripheral thermal afferent input arriving over ascending pathways. As noted, periventricular fibers constitute the medial pathway, while the medial forebrain bundle form the lateral pathway. Early in vivo electrophysiological studies indicate that it is the PO/AH warm-sensitive and cold-sensitive neurons (but not the temperature-insensitive neurons) that receive synaptic input from peripheral thermoreceptor pathways (6, 19, 26). However, because these studies employed extracellular recordings rather than intracellular recordings, distinctions could not be made between neurons having intrinsic thermosensitivity compared with EPSP-driven neurons having synaptically derived thermosensitivity. Therefore, it is possible that both warm-sensitive neurons and EPSP-driven neurons integrate information about central and peripheral temperatures.

Finally, Fig. 6 shows the morphology of a fourth neuronal type, the silent neuron, which is another possible integrator of central and peripheral thermal information. Compared with other PO/AH neurons, silent neurons have larger cell bodies, more primary dendrites, and extensive dendritic trees that are oriented in all directions (i.e., medial-lateral, dorsal-ventral, and rostral-caudal) (18). This reinforces the suggestion that silent neurons are highly dependent on synaptic inputs from many different sources, including ascending afferent pathways and remote neural sites. Most of these inputs are cut in hypothalamic tissue slices, and, hence, this is a probable reason for the lack of spontaneous FRs when these neurons are recorded intracellularly in vitro. On the other hand, some intracellular recordings indicate that silent neurons receive IPSPs from nearby warm-sensitive neurons. Therefore, a population of these silent neurons may represent not only the cold-sensitive neurons recorded in numerous in vivo studies, but also the heat production effector neurons that Hammel proposed in his timeless model.

In conclusion, over the past 40 years, Hammel’s neuronal model has offered much to neurophysiologists and thermal physiologists. It has provided investigators in both fields a way to understand the mechanisms within the black boxes of “closed-loop” negative feedback control systems. It has given us an understanding of the neural counterparts of error comparators, reference signals, and set points. It has provided an explanation of how endogenous factors and environmental conditions can influence and “adjust” Tset. Now, with continued electrophysiological, morphological, and immunohistochemical studies, the neuronal networks hypothesized by H. T. Hammel can be explored in even greater detail.

The concepts in Hammel’s model are applicable beyond thermoregulation. Homeostasis is the summation of several interrelated regulatory systems (i.e., body temperature, body water and metabolites, blood pressure, reproductive and metabolic hormones) (7,8). Hypothalamic neuronal networks play important roles in these regulations, and there is much overlap between different regulatory systems. In many respects, Hammel’s neuronal model is applicable to all of these homeostatic systems, since each system has its own regulated set points. The model can provide a mechanistic explanation for these set points using antagonistic synapses from sensitive and insensitive neurons. Moreover, Hammel’s model can suggest how neurons with multiple sensitivities can account for interactions between the different regulatory systems that encompass homeostasis.

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