Preoptic thermoregulatory mechanisms in detail

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THE MAMMALIAN BRAIN COORDINATES a range of behavioral and autonomic control mechanisms that together regulate body temperature. These mechanisms are engaged in response to temperature perturbations, which may be sensed by either cutaneous or deep body thermal sensors. Key to these thermoregulatory processes are neurons in the anterior hypothalamic-preoptic area (POA) (10). This region contains neurons with intrinsic temperature sensitivity and with the efferent connections to drive many (but not all) thermoregulatory effector mechanisms.

It has been apparent for some years, however, that thermoregulatory control mechanisms are multiple rather than unitary. This was evident from studies in rats where several behavioral responses to heating (operant choice of ambient temperature, locomotion, and grooming) survived lesions of the POA, whereas autonomic thermoregulatory responses were substantially disabled (9). The temperature-sensitive cells that drive each response seem to be anatomically distinct. Local heating of the posterior hypothalamus, for example, causes grooming behavior (saliva spreading), yet local warming of the POA is necessary to cause salivation, on which this evaporative heat loss mechanism depends (5, 9). Evidence is now also emerging that within the POA, autonomic thermoregulatory responses are not unitary. Dissection of the decussations and efferent pathways controlling specific thermal effectors has led Kanosue and colleagues (4) to the striking conclusion that all those studied so far (vasodilatation, inhibition of shivering, thermal salivation) are entirely separate systems. That is, each thermoregulatory effector is driven by its own distinct temperature-sensitive cells (which may be intermingled with those of others but apparently do not crossstalk) and its own private output pathway. In this model, any functional coordination is a consequence of matched thermal thresholds rather than linked motor commands (4, 11). Whether this independence principle applies to all thermoregulatory responses controlled by the POA is not yet known. Either way, the task ahead of us is to define each thermoregulatory control pathway, effector by effector. This endeavor will be greatly helped by methods with good spatial resolution. A paper in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology indicates one way this may be achieved.

Taking as a starting point the previous observation that GABA applied to the POA in conscious animals raises body temperature (8), Osaka (7) set out to define the mechanisms and localize the neurons responsible. Reasoning that the effect could be due to increased heat production, he measured the metabolic rate in anesthetized, artificially ventilated rats by the continuous record of oxygen consumption. He found rapid, robust, and reproducible increases in oxygen consumption when small injections of either GABA or the GABAA agonist muscimol were made bilaterally into part of the POA, the dorsomedial preoptic area (DMPO). The responsive region on each side was ~1 mm in diameter, with an even smaller core from which strong responses were obtained. The increases in metabolism were accompanied by a substantial tachycardia and by tonic EMG activity in the femoral and neck muscles. These responses lasted for ~5 min after GABA injections and for somewhat longer after muscimol injections. Muscle relaxants blocked the EMG activity but had little effect on the increase in metabolism, whereas blockade of β-adrenergic receptors with propranolol mostly prevented both the increased oxygen consumption and the tachycardia. The increase in metabolism is thus attributable primarily to nonshivering thermogenesis by brown adipose tissue.

At this point one could ask what this constellation of responses to pharmacological manipulation of the brain has to do with the physiology of temperature regulation. In answer, Osaka showed that a virtually identical combination of responses—thermogenesis, tachycardia, and tonic EMG activation—was obtained when the trunk skin was cooled transiently by ~5°C. What is more, this similarity was no accident: the three cooling-induced responses could be entirely prevented by injection into the DMPO of the GABAA antagonist bicuculline (7).

What do these findings mean? First, nonshivering thermogenesis is held (as are also tachycardia and EMG activity) under tonic inhibition by DMPO neurons (cf. Ref. 3). These tonically active DMPO neurons, which may or may not be intrinsically temperature sensitive, are themselves subject to GABAAergic inhibition driven by skin cooling. The evidence of this last point gives a strong positive answer to the provocative title of a previous paper in this journal: “Does the preoptic anterior hypothalamus receive thermosensitive information?” (1). The answer is yes, at least for the neurons that regulate nonshivering thermogenesis. Second, this may be an instance where each preoptic neuron drives several effectors at once, acting in this case perhaps via synaptic connections in the medullary raphe (2, 6). Finally, this elegant series of experiments shows an example of how to construct a fine-grained map of central neurons controlling a defined thermoregulatory effector. Corresponding maps now need to be made for other thermoregulatory effectors. It will be interesting to see how far they overlap with the distribution described here or whether they are anatomically distinct. Detailed functional anatomy of this type may be a powerful tool to dissect the central organization of thermoregulatory functions.

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REFERENCES