BAT control shows the way: medullary raphé/parapyramidal neurons and sympathetic regulation of brown adipose tissue

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In this issue of the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology, Cao and Morrison (6) show that the rise in body temperature elicited by fentanyl (a µ-opioid receptor agonist) in chloralose-urethane-anesthetized rats is associated with increased discharge of postganglionic sympathetic nerves supplying brown adipose tissue (BAT). Renal sympathetic discharge was also activated. Chemical inhibition of neuronal function in raphé pallidus, in the rostral ventral midline medulla oblongata, prevented the increase in BAT sympathetic discharge but not the increase in renal sympathetic discharge. The findings suggest that the net outcome of fentanyl-mediated stimulation of µ-opioid receptors in the forebrain, via a pathway that includes the dorsomedial hypothalamus (DMH), is excitation of medullary raphé neurons with excitatory input to BAT sympathetic preganglionic neurons in the spinal cord.

The findings are not of immediate clinical relevance. Indeed my understanding is that in clinical anesthesia practice, fentanyl is on a par with other anesthetic agents as far as effects on body temperature are concerned (there is usually a small fall in body temperature soon after induction, probably due to increased heat loss). However, the study (6) is an important addition to a very significant series from Morrison’s laboratory using the technique of multiunit electrophysiological recordings from postganglionic sympathetic nerves innervating BAT and/or the heart in anesthetized rats to investigate central nervous system (CNS) control of the raphé and more rostral brain regions (5, 7, 18, 21–30).

Morrison’s discovery that raphé neurons control BAT metabolism is the first to link the activity of a group of premotor sympathetic neurons with a noncardiovascular physiological function. The present consensus is that as well as regulating BAT metabolism, rostral medullary raphé/parapyramidal neurons control heart rate and blood supply to the cutaneous vascular bed, functions also related to thermoregulation. Thus the DMH-raphé/parapyramidal connection is also an important mediator of stress-induced tachycardia (43, 53, 54), findings that might elucidate CNS pathways underlying sympathetically mediated stress-induced cardiac arrhythmias, an important cause of sudden death in humans. Thus a vital role for raphé/parapyramidal neurons in controlling sympathetic regulation of the cutaneous circulation (1–3, 16, 33–40, 46) is consistent with the importance of the cutaneous vasculature in the cardiovascular responses to external stresses (52) in addition to its importance in heat exchange as part of temperature regulation (we go pale with fright). Given that BAT activation, cutaneous vasoconstriction, and cardiac changes are prominent responses to pain and stress, it will be interesting to see how neural regulation of these changes by the raphé/parapyramidal region will be integrated with work investigating the nociceptive/antinociceptive role of the rostral ventromedial medulla (RVM) (10, 20), since the two regions overlap. It may be that neurons in this region are particularly concerned with the regulation of cardiovascular/visceral processes relevant to our interactions with the external environment.

These discoveries come at a time when the forebrain-brainstem spinal cord neuroanatomical jigsaw is being pieced together. The paraventricular nucleus of the hypothalamus is in limbo status (temporarily presumably) while the dorsomedial hypothalamus (DMH) is running hot, with studies of forebrain control of BAT, heart rate, and/or cutaneous blood flow via the DMH-raphé/pyramidal axis in the rat from the laboratories of Morrison (see above), DiMicco (9, 41, 42), Dampney (11, 14), and in the rabbit from my laboratory (34). The traditional CNS core-temperature monitoring site, the “anterior hypothalamic-preoptic area,” is being deconstructed, with establishment of the interrelationships of its subunits with the DMH and other regions, including still-to-be-defined midbrain centers that link body temperature with sleep, eating, and other daily life activities (8, 12, 17, 19, 47, 50, 51).

These new findings command attention from colleagues who are expert on the intricate details of BAT function but evidently require further encouragement to critically evaluate the neuroanatomical circuitry mediating brain control of BAT. The recent review by Cannon and Nedergaard (4) is a landmark critical compendium of knowledge concerning BAT, but the section on CNS regulatory pathways gives credence to a theory that assumes spinal projections from the inferior olivary nucleus.

The productive outcome from Morrison’s focus on a noncardiovascular end organ reminds us how little is known concerning premotor sympathetic neurons regulating other noncardiovascular “autonomic” functions. Which hypothalamo-brain stem premotor sympathetic neurons regulate pupillary and eyelid functions (wide-eyed with fear)? Tache and colleagues have identified lower brain stem neurons regulating vagal discharge to the stomach and upper intestine (45, 48, 49), but what about lower brain stem/hypothalamic regulation of gut secretion, absorption, and motility via the sympathetic innervation? What about the hair follicles, the salivary glands, the thyroid, the liver, the spleen? What about specific sympathetically regulated renal functions apart from the general contribution of renal vascular resistance to arterial pressure? The list of relevant functions includes premotor sympathetic regulation of hematological and immunological tissues. How much is known of the premotor sympathetic neurons regulating genital function? Even if Walter Cannon (or the parody of Cannon) is correct and “everything goes off at once,” we would still need to characterize the transmitters and neural
connectivity of the relevant premotor sympathetic neurons. Thus the papers of Morrison and colleagues are important because they show the way for investigating sympathetic regulation of other noncardiovascular functions.

Activated BAT is responsible for more than one-half of total bodily oxygen consumption (4). Thus when BAT is activated via the sympathetic pathway, there is presumably also redirection of cardiac output to BAT via neurally mediated and/or local mechanisms. Morrison’s demonstration of coactivation of BAT and heart rate via raphé-regulated sympathetic pathways is thus potentially of major physiological relevance. Although blood flow to BAT has rarely been quantitated in the conscious animal, cold-induced increases in flow to BAT have been shown to be reduced by propranolol, suggesting a role (evidently a vasodilatory role) for the sympathetic innervation (32). As yet there is no evidence of a role for raphé-para-hippocampal neurons in sympathetic regulation of this process. We can await further developments on this most interesting front.

Morrison’s approach, measurement of BAT sympathetic activity in anesthetized rats, has obvious limitations. Resting discharge, necessary to identify the sympathetic nerves during recording, is minimal or absent unless the animal is cooled to 34–35°C. There is the possibility of mixed function in the nerves supplying BAT, particularly if it turns out that the vessels supplying BAT are sympathetically regulated. There is no guarantee that BAT vascular nerves have cardiac-related or other rhythms that might differentiate them electrophysiologically from similar nerves regulating BAT metabolism. The paper in this issue provides strong evidence that fentanyl-mediated µ-opioid receptor activation activates BAT sympathetic discharge. In contrast, as discussed by Cao and Morrison (6), an earlier study in conscious rats showed that BAT temperature did not increase more than body temperature in response to a similar stimulus, evidence against activation of BAT sympathetic nerves. Further experiments are required. Such discrepancies emphasize the importance of using different techniques to investigate a particular problem. Characterizing the conditions under which BAT is activated in conscious freely moving animals and describing the underlying central and peripheral neural mechanisms is clearly the ultimate goal.

Histological documentation of intramedullary injection and stimulation sites is strongly emphasized in the papers from Morrison’s laboratory. It is a pleasure to see these sites documented by photomicrographs of the actual tissue sections, rather than by a series of dots on standard sections from an atlas (“this looks like a similar spot”). However, I disagree with Morrison’s near exclusive focus on the small ventral midline neurons present in the area that has come to be defined as raphé pallidus. The term “pallidus” was applied to midline raphé neurons with pale Nissl substance (44). The “magnus” property was ascribed to the more obvious larger group of neurons at the rostral pole of the medullary raphé, not to the size of individual neurons. Neuroanatomic studies have not demonstrated systematic differences between neurons in raphé pallidus and other small neurons scattered around, and sometimes within, the pyramids, including those in the subependymal zone just lateral to the pyramids. Dentrites of neurons spread for some distance, and substances injected into the raphé/para-hippocampal region tend to spread over the pyramidal tracts, and then ventrally toward the surface of the medulla. In rabbits, ear pinna sympathetic discharge activated from the raphé/para-hippocampal region just lateral to the pyramids is as vigorous as the discharge elicited from the midline raphé pallidus itself (35). So I suspect that the neurons responsible for BAT activation are distributed through the more ventral portions of the raphé/para-hippocampal region.

These BAT-regulating raphé/para-hippocampal neurons remain to be identified. There are, as yet, no inputs to the neurons that can be used to define them electrophysiologically when they are antidromically activated from the spinal cord (as baroreceptor-derived inputs can be used to define RVLM cardiovascular neurons). Cao and Morrison (7) used orthograde techniques to show that the BAT-controlling spinally projecting axons have very low conduction velocities (<0.5 m/s) in rats, suggesting that they are unmyelinated. Local intra-raphé injection of a 5-hydroxytryptamine1A (5-HT1A) agonist profoundly inhibits the responsible perikarya, a response reversible with a 5-HT1A antagonist and therefore mediated by activation of 5-HT1A receptors (21). This might suggest that unmyelinated bulbospinal 5-HT-synthesizing neurons contribute to the BAT-regulatory function. However, this conclusion is “on hold” at present. The limited information we have indicates that there are 5-HT1A receptors on both 5-HT-containing and non-5-HT-containing raphé/para-hippocampal neurons (13), as has also been demonstrated for the dorsal raphé in the midbrain (15). Nakamura and colleagues (31) have argued vigorously against the importance of 5-HT as a relevant neurotransmitter in raphé/para-hippocampal BAT regulatory neurons. After injection of pseudorabies virus into BAT, large numbers of virus-positive raphé/para-hippocampal neurons contain vesicular glutamate transporter 3 (VGLUT3), with little overlap with 5-HT-containing neurons. In anesthetized rats, blockade of excitatory amino acid receptors in the spinal cord prevented raphé-induced BAT activation, suggesting that glutamate is an important transmitter in the BAT regulating raphé/para-hippocampal neurons. However, other studies also showed that many virus-positive neurons express receptors for PGE3, a property indicating that a substantial population of raphé/para-hippocampal neurons regulating BAT metabolism might be 5-HT-containing neurons (30a, 51). Drugs that interact with 5-HT1A and 5-HT2A receptors have major effects on cutaneous blood flow (35,36). Time will tell which neurotransmitter agents, singly or in combination, are important for raphé/para-hippocampal control of BAT, cutaneous blood flow, and heart rate in the various natural physiological situations.

Morrison and colleagues investigate acute events in anesthetized animals. The raphé/para-hippocampal neurons on which they focus are on the effenter side of the central thermoregulatory neural pathways, contributing both to heat production (BAT) and heat exchange with the environment (the cutaneous circulation). This means that the concept of a temperature “set point” has minimal relevance to their studies. It is, however, interesting to notice that with advances in our knowledge of the different neural pathways mediating various aspects of temperature regulation, the traditional “set point” seems a much less constructive focus for our studies. In my view the conceptual framework of the various set points (thermoregulatory, arterial pressure, etc.) assumes a too-passive brain, with postulated control systems responding by fixed rules to negate the effects of disturbing “pokes” from the environment. In fact, many of the different activities that make up our daily life involve changes in temperature-related processes. These changes are...
regulated simultaneously by in-built brain programs, central commands that operate in an integrated manner, not by individual control processes correcting deviations from a set point. No doubt future studies will establish that the raphe/parapyramidal BAT-regulating neurons have complex integrative actions, so that their contribution to thermoregulatory control is more than that of a lower brain stem relay for more rostrally integrated neural signals, a role established by Morrison and colleagues. But the discovery of even this is a significant step forward, a permanent contribution to physiology.

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