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Update article

Sympathetic premotor neurons mediating thermoregulatory functions

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Abstract

The sympathetic nervous system controls various homeostatic conditions, such as blood circulation, body temperature, and energy expenditure, through the regulation of diverse peripheral effector organs. In this system, sympathetic premotor neurons play a crucial role by mediating efferent signals from higher autonomic centers directly to sympathetic preganglionic neurons in the intermediolateral cell column of the spinal cord. The medulla oblongata is thought to subsume many sympathetic premotor neurons, and the rostral ventrolateral medulla (RVLM) has been established to contain the sympathetic premotor neurons responsible for cardiovascular control. Although premotor neurons controlling other effector organs than the cardiovascular system have been largely unknown, recent accumulating findings have suggested that medullary raphe regions including the raphe pallidus and raphe magnus nuclei are candidates for the pools of excitatory sympathetic premotor neurons involved in thermoregulation. Further recently, excitatory premotor neurons controlling the thermoregulatory effector organs, brown adipose tissue and tail, have been identified with expression of vesicular glutamate transporter (VGLUT)3, whereas those for cardiovascular control were characterized with VGLUT2 expression. The VGLUT3-expressing premotor neurons would mediate thermoregulation including fever induction, and could be also involved in the control of energy metabolism.

Keywords: Cardiovascular system; Fever; Medulla oblongata; Obesity; Thermoregulation; Prostaglandin E_2; Sympathetic nervous system; Vesicular glutamate transporter

1. Introduction

The sympathetic nervous system homeostatically controls diverse body conditions of animals, such as blood circulation, body temperature, and energy metabolism, collaborating with the parasympathetic system. The autonomic center in the brain, mostly located in the hypothalamus, collects information on the changes of body conditions, and sends counteracting command signals to peripheral effector organs through final output neurons (visceromotor neurons), i.e. sympathetic preganglionic neurons (SPNs), which are located in the intermediolateral cell column (IML) of the thoracic spinal cord. In these descending command pathways, sympathetic premotor neurons, which directly innervate and control SPNs, are considered to play a pivotal role in the transmission of the central command signals to SPNs and probably in some integration of the peripheral sensory inputs and central command signals, as premotor neurons in the skeletomotor system. Thus, identification and characterization of sympathetic premotor neurons are important to understand the execution and integration mechanisms of the sympathetic nervous system.

Several brain regions have been considered as candidates for the pools of sympathetic premotor neurons on the basis of the anatomical observations in transneuronal tracing after

Abbreviations: BAT, Brown adipose tissue; DMH, Dorsomedial hypothalamic nucleus; IML, Intermediolateral cell column; PG, Prostaglandin; POA, Preoptic area; PRV, Pseudorabies virus; RMg, Raphe magnus nucleus; RPa, Raphe pallidus nucleus; rRPa, Rostral part of the raphe pallidus nucleus; RVLM, Rostral ventrolateral medulla; SPN, Sympathetic preganglionic neuron; VGLUT, Vesicular glutamate transporter

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inoculation of pseudorabies virus (PRV) into peripheral effector organs (Strack et al., 1989; Schramm et al., 1993; Jansen et al., 1995; Bamshad et al., 1998; Smith et al., 1998; Bamshad et al., 1999). Of those brain regions, the rostral ventrolateral medulla (RVLM) is the most established one that contains sympathetic premotor neurons for the control of the cardiovascular system (Dampney, 1994). In addition, the RVLM is involved in the sympathetic control of the adrenal medulla (Leman et al., 2000; Morrison and Cao, 2000), and adrenaline and noradrenaline released from the adrenal medulla into the blood circulation could affect functions of diverse peripheral organs. However, RVLM premotor activity scarcely contributes to the neural control of a group of sympathetic effector organs, such as the pupil, nictitating membrane, gut, brown adipose tissue (BAT), and rat tail artery (McAllen et al., 1982; McAllen, 1986; Morrison, 1999; Rathner and McAllen, 1999). Thus, there might be, in the supraspinal regions, other populations of sympathetic premotor neurons that are involved in the control of these effector organs.

Recently, several lines of evidence have shown that neurons in medullary raphe regions mediate thermoregulatory and fever-inducing command signals, and that excitatory neurons in these raphe regions are responsive to thermogenic stimuli and directly project to SPNs. Here, we summarize the recent findings on the thermoregulatory sympathetic premotor neurons in medullary raphe regions, and discuss the central descending pathways for thermoregulation including fever induction.

2. Critical roles of medullary raphe regions in thermoregulatory functions

The sympathetic nervous system regulates body temperature by controlling thermogenesis and heat loss in peripheral effector organs. In rodents, BAT is a principal organ for non-shivering thermogenesis (Rothwell, 1992), and the tail in rats and ear pinna in rabbits function as a heat-dissipating organ through the regulation of cutaneous blood flow by vasoconstriction (Grant, 1935; Gordon, 1990). We first describe recent findings from anatomical and physiological studies suggesting that sympathetic premotor neurons specific to these thermoregulatory effector organs are distributed in rostral medullary raphe regions.

Our research group first investigated neuronal activation in rat ventral medullary regions in response to pyrogenic stimuli by immunohistochemically detecting the expression of Fos protein (Nakamura et al., 2002). Pyrogenic stimuli have been good experimental cues to investigate the central mechanism for sympathetic thermoregulation. The first step of pyrogenic neurotransmission in the brain is thought to be a triggering action of the endogenous pyrogenic mediator, prostaglandin (PG) E_2, in the preoptic area (POA) (Feldberg and Saxena, 1971; Stitt, 1973; Williams et al., 1977). PGE_2 application into the lateral ventricle or the POA induced thermogenesis in the interscapular BAT and fever (rise in rectal temperature), and also triggered the activation of neurons in the rostral medullary raphe regions consisting of the rostral part of the raphe pallidus nucleus (rRPa) and the raphe magnus nucleus (RMg), most of these activated neurons being negative for serotonin immunoreactivity (Nakamura et al., 2002). Furthermore, suppression of the rRPa and RMg with microinjection of muscimol, a $GABA_A$ receptor agonist, abolished the PGE_2-induced BAT thermogenesis or fever (Fig. 1a and b; Nakamura et al., 2002; Morrison, 2003). These results indicate that the rRPa and RMg contain a group of neurons that essentially mediate the transmission of pyrogenic signals triggered by PGE_2 from the POA to SPNs, and these medullary raphe neurons may be the sympathetic premotor neurons for fever induction. Recent recording of cutaneous sympathetic activity in the rat tail by Korsak and Gilbey (2004) showed that the activity was markedly increased following central PGE_1 application, and this increase was attenuated by microinjection of GABA into the rRPa and RMg. Thus, the fever-mediating medullary raphe neurons could be also involved in the fever-associated reduction in heat dissipation through cutaneous vasoconstriction.

The involvement of these medullary raphe regions in the sympathetic control of multiple thermoregulatory effector organs is supported by several reports that stimulation or disinhibition of these raphe regions increased the efferent sympathetic activity to rat interscapular BAT, rat tail artery, and rabbit ear pinna blood vessels (Blessing et al., 1999; Morrison, 1999; Morrison et al., 1999; Rathner and McAllen, 1999; Blessing and Nalivaiko, 2001). Furthermore, suppression of the raphe pallidus nucleus (RPa) with muscimol microinjection caused hypothermia (Zaretsky et al., 2003a), and neurons in these raphe regions expressed Fos in response to cold exposure of rats (Bonaz and Taché, 1994; Morrison et al., 1999; Nakamura et al., 2004a). Collectively, it is indicated that these medullary raphe regions are crucial for the sympathetic control of normothermic body temperature as well as for fever induction and contain neurons whose activation under low ambient temperature and febrile states leads to stimulation of the sympathetic nerve activity to thermoregulatory effector organs.

3. Localization of glutamatergic axon terminals in the IML

The medullary raphe regions are known to contain neurons projecting to the IML (Loewy, 1981), and in vivo electrophysiological recordings revealed the existence of spinally projecting medullary raphe neurons that were activated by cold exposure (Rathner et al., 2001). If the thermoregulatory neurons in the medullary raphe regions directly innervate and control SPNs as sympathetic premotor neurons, these medullary raphe neurons would be excitatory, probably glutamatergic, and axon terminals from these