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Review

Neurochemistry of bulbospinal presympathetic neurons of the medulla oblongata

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ABSTRACT

This review focuses on presympathetic neurons in the medulla oblongata including the adrenergic cell groups C1–C3 in the rostral ventrolateral medulla and the serotonergic, GABAergic and glycinergic neurons in the ventromedial medulla. The phenotypes of these neurons including colocalized neuropeptides (e.g., neuropeptide Y, enkephalin, thyrotropin-releasing hormone, substance P) as well as their relative anatomical location are considered in relation to predicting their function in control of sympathetic outflow, in particular the sympathetic outflows controlling blood pressure and thermoregulation. Several explanations are considered for how the neuroeffectors coexisting in these neurons might be functioning, although their exact purpose remains unknown. Although there is abundant data on potential neurotransmitters and neuropeptides contained in the presympathetic neurons, we are still unable to predict function and physiology based solely on the phenotype of these neurons.

Contents

Abbreviations: 5HT, 5-hydoxytryptamine (serotonin); Cal, calbindin; CART, cocaine- and amphetamine-regulated transcript; DBH, dopamine-beta-hydroxylase; ENK, enkephalin; EPSP, excitatory postsynaptic potential; GAD, glutamic acid decarboxylase; GLY, glycine; ir, immunoreactive; IML, intermediolateral cell column; IPSP, inhibitory postsynaptic potential; NPY, neuropeptide Y; PACAP, pituitary adenylate cyclase-activating polypeptide; PNMT, phenylethanolamine-N-methyltransferase; PRV, pseudorabies virus; RVLM, rostral ventrolateral medulla; RVMM, rostral ventromedial medulla; SPGNs, sympathetic preganglionic neurons; SubP, substance P; TH, tyrosine hydroxylase; TRH, thyrotropin-releasing hormone; VGLUT, vesicular glutamate transporter.

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1. Introduction

The neurons that innervate the spinal sympathetic preganglionic neurons (SPGNs) are termed presympathetic neurons. The SPGNs are the final common pathway for many reflexes important to homeostasis (e.g., maintaining blood pressure or body temperature at appropriate levels). Thus the presympathetic neurons are in the position to orchestrate these reflexes. Presympathetic neurons are located in the upper cervical spinal cord, medulla, pons and hypothalamus. This review will focus on the neurotransmitters and peptides associated with the presympathetic neurons located in the medulla oblongata and what the various phenotypes of these neurons might reveal about sympathetic control, with particular focus on cardiovascular control and thermoregulation.

2. Bulbospinal presympathetic neurons

The sympathetic nervous system is responsible for "resting state" homeostatic functions as well as responding to stressful conditions such as exercise, disease or "fight or flight" situations. These functions are orchestrated through a complex network operating through SPGNs in the spinal cord that project to sympathetic ganglia. The neurons directly innervating the SPGNs are the presympathetic neurons. The presympathetic neurons are in the position to control a range of functions from blood pressure to bladder control. This review will focus on the presympathetic neurons in the medulla oblongata that control primarily cardiovascular and thermoregulatory functions.

Jansen et al. (1995a) and Jansen and Loewy (1997) found many groups of presympathetic neurons in the upper cervical spinal cord, medulla, pons and forebrain using the pseudorabies virus (PRV). The PRV is taken up by cells in a post-ganglionic target (e.g., adrenal gland or heart), replicates within the cell and then buds out and infects the next cell(s) in closest physical proximity, that is those that are synaptically connected (Card et al., 1990). This cycle of replication and infection continues through chains of synaptically connected neurons, thus revealing the sympathetic preganglionic neurons, sympathetic interneurons within the spinal cord (not normally referred to as "presympathetic" although they are directly antecedent to SPGNs) and the presympathetic neurons in the brainstem (as well as pons and forebrain). This method is useful in determining candidate presympathetic neurons and has identified the main groups of these presympathetic neurons in the medulla: the rostral ventrolateral medulla (RVLM) that contains the C1 cells, the rostral ventromedial medulla (RVMM) with the various raphe nuclei and the dorsal area around the medial longitudinal fasciculus/lateral tegmental field containing the C3 neurons. These groups of neurons will be discussed by primary phenotype and function.

3. RVLM presympathetic neurons

3.1. Catecholaminergic presympathetic RVLM neurons, the C1 cells

Fuxe and coworkers introduced the first technique that allowed identification of various monoaminergic neurons in brain and showed that some of these neurons had spinal projections (Carlsson et al., 1964; Dahlstrom and Fuxe, 1965). The C1 adrenergic neurons were first described by Hokfelt et al. (1974) who also suggested that C1 cells might be involved in vasomotor control (Bolme et al., 1974). The defining characteristic of these neurons is that they contain the catecholamine synthetic enzymes necessary for the production of epinephrine, i.e., tyrosine hydroxylase (TH), dopamine beta-hydroxylase (DBH) and phenylethanolamine-N-methyltransferase (PNMT). The first demonstration that C1 neurons contain all the catecholamine synthetic enzymes was only relatively recently demonstrated by Phillips et al. (2001).

Reis and coworkers added substantially to the hypothesis that the C1 cells were presympathetic by identifying the spinally projecting PNMT-immunoreactive (ir) C1 neurons in the ventrolateral medulla and showing that PNMT terminals contact the SPGNs in rat (Tucker et al., 1987; Milner et al., 1988). Anderson et al. (1989) and Bernstein-Goral and Bohn (1989) replicated these findings of PNMT terminals in contact with SPGNs in the rat. Minson et al. (1990) added more evidence for C1 bulbospinal neurons and found that some of the PNMT innervation of the spinal cord comes from the more dorsal C2 and C3 adrenergic neurons (discussed in more detail below).

3.2. Other neuroactive substances present in C1 neurons

The RVLM C1 bulbospinal neurons contain several other neurochemicals including enkephalin (Stornetta et al., 2001), NPY (Blessing et al., 1987; Tseng et al., 1993; Stornetta et al., 1999), cocaine- and amphetamine-regulated transcript (CART) (Dun et al., 2002; Burman et al., 2004), pre-pro-tachykinin (substance P) (Li et al., 2005) and calbindin (Goodchild et al., 2000). The colocalization of potential transmitter substances in the C1 cells has been previously reviewed by Pilowsky and Goodchild (2002). The most recently described potential transmitter found to be colocalized in the C1 neurons is the sympatho-excitatory neurochemical pituitary adenylate cyclase-activating polypeptide (PACAP) (Farnham et al., 2008).

To date, the phenotypic identification of cotransmitters in C1 neurons has yielded some limited predictive value on the projection pattern and conduction velocity of C1 cells with specific colocalized neuropeptides. One instance is that NPY tends to be in the C1 neurons projecting to the hypothalamus rather than to the spinal cord (only 10% of spinally projecting C1 cells contain NPY where 96% of C1 cells projecting to hypothalamus are NPY positive (Stornetta et al., 1999)). Although C1 neurons have a variety of conduction velocities, from a faster conduction suggestive of lightly myelinated axons to a slower conduction velocity associated with unmyelinated axons, there is some correlation of the colocalized peptide in C1 neurons with their conduction velocity. The C1-NPY neurons have a slow conduction velocity (Stornetta et al., 1999) while enkephalin containing C1 neurons tend to have a faster conduction velocity than non-enkephalinergic C1 cells (Stornetta et al., 2001).

We know something of the effects of some of these colocalized neuropeptides on SPGNs. For instance, using the technique of direct iontophoresis or pressure ejection onto identified neurons, substance P increased the firing rate of SPGNs (Gilbey et al., 1983; Backman and Henry, 1984; Dun and Mo, 1988; Backman et al., 1990). PACAP excites SPGNs (Lai et al., 1997) by directly potentiating NMDA-receptor-mediated responses (Wu and Dun, 1997). Although enkephalin itself has not been directly tested, another opiate, morphine, inhibits the activity of SPGNs (Guyenet and Stornetta, 1982) consistent with the generally inhibitory effect of enkephalin elsewhere in the CNS.

CART is excitatory to SPGNs (if one assumes that intrathecal application and measurement of blood pressure and heart rate are indicative of a direct effect on SPGNs), since CART applied intrathecally caused sympathoactivation at nanomolar concentrations, while at lower concentrations, CART dramatically increased the cardiovascular effects of intrathecal glutamate (Scruggs et al., 2005; Dun et al., 2007). The effects of intrathecal injections of NPY are variable depending on concentration (nanomolar concentrations produce pressor responses (Hassessian et al., 1990; Wager-Page et al., 1993) while sub-nanomolar concentrations produce