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Review Article

Neuropeptides and the Central Neural Regulation of the Cardiorespiratory System

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Abstract

This review considers the role played by neuropeptides which, unlike GABA and glutamate (acting at ligand-gated ion channels), modulate cardiorespiratory reflexes slowly through metabotropic receptors. Our findings reveal that reflexes may be differentially modulated so that depending on which neuropeptide agonist is microinjected into the rostral ventrolateral medulla, differential effects on reflexes are observed. This means that, for example, the mu opioid agonist DAMGO will attenuate the sympathetic baroreflex but not the somatosympathetic reflex. On the other hand, the delta agonist DPDPE attenuates the somatosympathetic reflex but has no effect on baroreflex function. These, and other data with other peptides, suggest that neuropeptides may play a crucial role in the modulation of different adaptive reflexes. [*Tzu Chi Med J* 2009;21(2):99–102]

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1. Introduction

Central regulation of cardiorespiratory function is the basis of our scientific knowledge of critical care medicine. Despite this, the neuronal pathways, reflexes [1], generators of tonic activity [2–4], neurotransmitters [3,5–10] and regulators of intracellular control mechanisms [11–13] are only now coming into focus following three to four decades of investigation from our own work (see above) and that of others (e.g., see references 14–18). More recently, attention is being focused on interactions between systems at a central level. Again, although known to exist for sometime [19], interactions between systems are only now being studied in detail [20]. What is the significance of studying all of these features of neuronal interaction in systems that are important for central cardiorespiratory regulation?

At a basic level, we are concerned with the temporal, frequency and structural aspects of neuronal control that influence the tonic regulation of airways, breathing and circulation. Together, these features dictate how often and when a neuron fires, which of its complement of neurotransmitters are released and if this release can exert plastic changes to strengthen the connections between neurons. Features such as firing frequency may have quite complex effects. Early studies from Guyenet's laboratory on presympathetic neurons clearly revealed a frequency-dependent effect on action potential amplitude. Presumably, such changes affect neurotransmitter quantities released at the synapse. Frequency dependence of neurotransmitter release is a well known phenomenon and it was recently reported to be due to size exclusion at release sites in adrenal chromaffin cells [21]. Use of dependent structural changes at synapses is well known in many nervous systems (22). Taken together, these features of neuronal interaction demonstrate that simple electrical wiring diagrams, although useful starting points, are not adequate for describing the full dynamic range of neuronal interactions.

2. Cardiorespiratory pathways

Space does not allow a full description of brainstem and spinal cord cardiovascular and respiratory regulation. The broad details of these have been expertly addressed in several recent reviews and books (1,20,23,24). Broadly, within the brainstem are presympathetic neurons (PSN) whose coordinated activity leads to the generation of tonic activity (25), which is in turn transmitted via bulbospinal axons to sympathetic preganglionic neurons (SPN—because their axons enter ganglia) in the thoracolumbar spinal cord. There are some differences in the locations and mixing of SPN in vertebrates, but in mammals the SPN are mostly found in the intermediolateral nuclei. SPN at different levels innervate different sympathetic post-ganglionic neurons (SPGN—because their axons are found exiting ganglia). On top of this tonic activity, higher centers and adaptive reflexes including the baroreceptor and somatosympathetic reflexes, exert a modulatory effect. Apart from any inherent tone present within PSN, two key influences regulate sympathetic activity: respiratory activity and baroreceptor inputs. The importance of respiratory inputs in the conscious state cannot be underestimated (26). Tonic respiratory activity in the rat is localized to a small region termed the preBötzinger complex (preBötC). The preBötC is located in ventral brainstem dorsal to the rostral ventrolateral medulla but caudal to the Bötzinger neurons. It was originally described in neonatal rat as the minimal region from which respiratory-like nerve activity could be generated (27), but a homologous region is present in adult rat (28). This region is crucial for the initiation of respiratory activity in eupneic conditions. Destruction of it with agents such as substance P-saporin have profound effects on respiratory rhythm generation (29). From this site, the respiratory rhythm is transmitted, transformed and appropriately altered to permit many of the activities associated with normal respiration, including vocal cord opening and diaphragmatic contraction during inspiration.

3. Role of neuropeptides

Most of the neurotransmission that occurs in the central nervous system appears to require the obligatory release of excitatory (e.g., glutamate) or inhibitory (GABA and glycine) amino acid neurotransmitters. Certainly, blockade of excitatory neurotransmission in the caudal ventrolateral medulla will entirely block the baroreceptor reflex (30) and modulate respiratory activity (31). Despite this clearly crucial and obligatory role for rapidly acting neurotransmitters that exert their effects through ligand-gated receptors and rapid modulation of Na^+, Cl^-, K^+ and Ca^{++} conductances with consequent changes in membrane potential in the millisecond time range, other neurotransmitters exert effects that may be even more potent and occur over longer time frames. Such neurotransmitters—of which the neuropeptides are surely a classic example—exert their effects through actions on, amongst others, 7-transmembrane spanning receptors, that are coupled to many second messenger systems including kinases and G-proteins. Recently, it was reported that in primary sensory neurons, substance P suppresses GABA-A receptor function by activation of protein kinase C (32,33). This mechanism was subsequently shown to occur in sympathetic regulatory neurons in the paraventricular nucleus (34). In our own studies, we have focused on the effects of neuropeptides on the activity and function of neurons in the PSN in the rostral ventrolateral medulla. This work revealed that mu opioid receptor activation suppresses splanchnic and lumbar sympathetic nerve activity and sympathetic baroreceptor function (decrease in slope and range) but has no effect on the somatosympathetic reflex (3). Delta opioid receptors are also present in the rostral ventrolateral medulla and appose sympathoexcitatory C1 neurons (6). Activation of delta receptors does not affect baroreceptor function but causes a significant decrement in the somatosympathetic reflex (3).

In addition to their presence in the preBötC, substance P (neurokinin 1) receptors are present throughout the ventral medulla (35). Like delta receptor activation, neurokinin 1 receptor activation selectively attenuates the somatosympathetic reflex without affecting other adaptive reflexes. We term this differential responsiveness of PSN "functional fingerprinting" as a corollary to "chemical coding".

As a cautionary note, it must be stated that our work is pharmacological so that we cannot be certain of the physiological role of the receptors that we agonize or antagonize. Similarly, one must be careful in interpreting studies that use substance P-saporin since such studies destroy the neuron without clearly indicating the function of the receptor. Perhaps future studies with RNA silencing will be more productive in this regard (36).

4. Conclusion

Studies of neuropeptides in the brainstem and spinal cord have revealed many new features about the way that cardiorespiratory regulation occurs. The use of activation of reflexes, either by electrical stimulation of nerves or by "naturalistic activation", combined with the measurement of multiple autonomic outputs, provides an extremely valuable method for interrogating the role that neurotransmitters of all types, including peptides, play in the control of the heart and blood vessels. It is to be hoped that approaches of this type will ultimately assist in the targeting of therapies for disorders such as hypertension.

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