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Review

# A new focus on interoceptive properties of adrenal medulla

Boris Mravec*

*Institute of Experimental Endocrinology, Slovak Academy of Sciences and Institute of Pathophysiology, Faculty of Medicine, Comenius University, Bratislava, Slovak Republic*

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**Abstract**

The adrenal medulla is an important part of the sympathoadrenal system. Chromaffin cells of the adrenal medulla respond to a broad spectrum of stressful situations by releasing epinephrine and norepinephrine. Originally, it was accepted that this response is controlled exclusively by central nervous system structures.

However, it was also demonstrated that a surgically denervated adrenal medulla can respond directly by secreting epinephrine and norepinephrine during an imbalance of internal environment (hypoglycemia, asphyxia). Published data had documented the innervation of the adrenal medulla by sensory neurons of spinal dorsal root ganglia. In addition, recent data showed that ganglion cells of the adrenal medulla project ascending axons. These data suggested potential transmission of information from the adrenal medulla to the central nervous system regarding metabolic changes in the blood.

This paper presents an overview of possible involvement of adrenal medullary chromaffin cells in the detection of changes in the internal environment and in the transmission of this information to the central nervous system.


*Keywords:* Adrenal medulla; Catecholamines; Chromaffin cells; Hypoglycemia; Hypoxia; Interoception

**Contents**



* Tel.: +421 2 54772800; fax: +421 2 54774247.
*E-mail address:* ueenmrav@savba.sk.

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## 1. Introduction

The adrenal medulla, an important endocrine organ, represents a part of the sympathoadrenal system (Kvetnansky and McCarty, 2000). Embryologically, it is derived from the same population of precursor of neural crest cells that will later constitute postganglionic neurons of the sympathoadrenal system (Pahlman and Hedborg, 2000; Huber et al., 2002; Kalcheim et al., 2002). Therefore, the adrenal medulla can be considered a derived sympathetic ganglion. Hence, it is not surprising that the responses of both adrenal medulla and sympathetic system to adequate stimuli are closely associated (Hickman, 2001).

Two types of chromaffin cells represent the major population of adrenal medullary cells, e.g., the epinephrine and norepinephrine cells secreting catecholamines directly to bloodstream (Hillarp and Hokfelt, 1953; Goldstein, 2001; Considine, 2004). In addition to chromaffin cells, there are also clusters of cells constituting ganglion-like structures (Coupland, 1965; Holgert et al., 1996).

According to the traditional view, the endocrine activity of the adrenal medulla is under predominant influence of central nervous system structures (Carlsson et al., 1992; Scislo et al., 1998; Morrison and Cao, 2000). On the other hand, there are clear data suggesting that adrenal medullary cells can respond directly to some types of perturbations of the internal environment (Khalil et al., 1986; Thompson et al., 1997). Possible transmission of interoceptive information by the adrenal medulla will be discussed below. This article represents an integration of established data and outlines of a proposed new field research into adrenal medullary function.

## 2. Afferent and efferent connection of adrenal medullary cells

### 2.1. Sympathetic innervation

The adrenal medulla receives axons of sympathetic preganglionic neurons (SPNs) originating from the intermediolateral cell column of $Th_4$ to $Th_{12}$ segments of the spinal cord via the splanchnic nerve (Fig. 1A; Coupland, 1971; Strack et al., 1988).

SPNs are functionally divided into the groups of neurons innervating either epinephrine- or norepinephrine-releasing adrenal chromaffin cells. This arrangement provides a basis identifying the different sympathetic networks underlying the differential regulation of epinephrine and norepinephrine secretion from the adrenal medulla in response to physiological challenges and experimental stimuli (Morrison and Cao, 2000). SPNs innervating the adrenal medulla are the principal sites integrating the information from both long- and short-loop feedback mechanisms.

Long loops represent the pathways originating in supraspinal centers, which receive somatic and visceral information from the periphery (Sun, 1995). The activity of SPNs which innervate adrenal medullary chromaffin cells is regulated by some areas of brain including caudal raphe nuclei, ventromedial medulla, rostral ventrolateral medulla, A5 cell group, and paraventricular hypothalamic nucleus (Strack et al., 1989).

Short loops represent the pathways carrying information via dorsal root ganglia directly to SPNs. Both long- and short-loop pathways can synapse either directly to SPNs or indirectly by local interneurons (Joshi et al., 1995).

Chromaffin cells are arranged in clusters surrounded by sparse connective tissue. Clusters of chromaffin cells, which

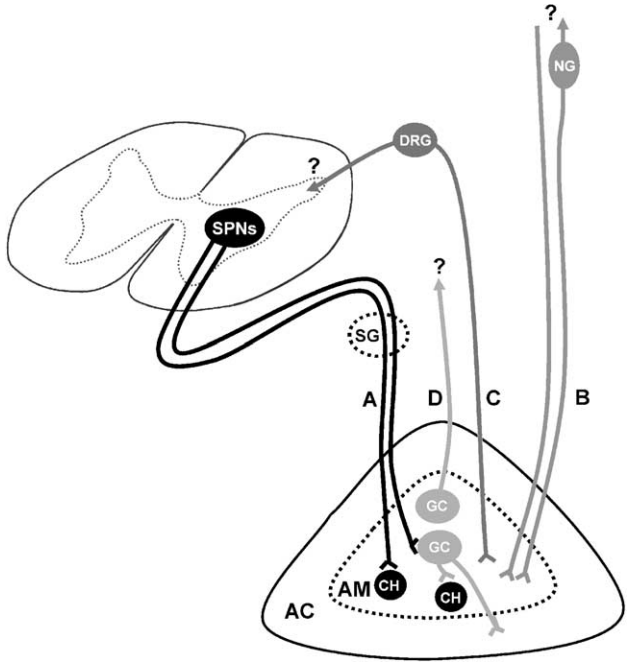


Fig. 1. Schematic drawing of adrenal medullary innervation. (A) Sympathetic innervation (splanchnic nerve). (B) Parasympathetic innervation (vagus nerve). (C) Sensory innervation. (D) Ascending axons from adrenal medullary ganglionic neurons. AC—adrenal cortex; AM—adrenal medulla; CH—chromaffin cells; DRG—dorsal root ganglion; GC—ganglion cells; NG—nodose ganglion; SG—sympathetic ganglion; SPNs—sympathetic preganglionic neurons; ?—unknown destination.