Neuropeptides 48 (2014) 65–73

Contents lists available at ScienceDirect

Neuropeptides

journal homepage: www.elsevier.com/locate/npep

# Blood borne hormones in a cross-talk between peripheral and brain mechanisms regulating blood pressure, the role of circumventricular organs

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ARTICLE INFO

*Article history:*
Received 31 May 2013
Accepted 10 January 2014
Available online 22 January 2014

*Keywords:*
Blood pressure
Circumventricular organs
Catecholamines
Angiotensin II
Vasopressin
Aldosterone
Natriuretic peptides
Endothelins
NPY
Bradykinin
Histamine
Acetylocholine

ABSTRACT

Accumulating evidence suggests that blood borne hormones modulate brain mechanisms regulating blood pressure. This appears to be mediated by the circumventricular organs which are located in the walls of the brain ventricular system and lack the blood–brain barrier. Recent evidence shows that neurons of the circumventricular organs express receptors for the majority of cardiovascular hormones. Intracerebroventricular infusions of hormones and their antagonists is one approach to evaluate the influence of blood borne hormones on the neural mechanisms regulating arterial blood pressure. Interestingly, there is no clear correlation between peripheral and central effects of cardiovascular hormones. For example, angiotensin II increases blood pressure acting peripherally and centrally, whereas peripherally acting pressor catecholamines decrease blood pressure when infused intracerebroventricularly. The physiological role of such dual hemodynamic responses has not yet been clarified.

In the paper we review studies on hemodynamic effects of catecholamines, neuropeptide Y, angiotensin II, aldosterone, natriuretic peptides, endothelins, histamine and bradykinin in the context of their role in a cross-talk between peripheral and brain mechanisms involved in the regulation of arterial blood pressure.



## 1. The brain and the regulation of arterial blood pressure

### 1.1. The regulation of arterial blood pressure

A major function of the circulatory system is to provide an adequate blood flow through the supplied tissues of the body. This would not be possible if it were not for the precise control of arterial blood pressure BP. Failure to maintain BP within narrow physiological limits may lead to either shock or hypertension, both associated with poor clinical outcome.

Mechanisms involved in the control of BP have been extensively described elsewhere (Guyton et al., 1981; Guyton, 2006). Traditionally, the regulation of BP involves mechanisms for short as well as long-term control. A main goal for the short-term control is to prevent sudden changes in BP via the effects of the nervous system on vascular capacitance and on cardiac pumping ability (Guyton, 2006), whereas the long term regulation of BP is thought to be dependent on blood volume regulated primarily by the kidneys, with little or no effect from the central nervous system.

However, the classical description of the mechanisms regulating BP in the long-term is currently under debate (Malpas, 2009; Montani and Van Vliet, 2009; Osborn, 2005; Ufnal, 2012) and recent evidence suggests that the role of the nervous system in the control of BP may need revision. There are several reasons for this. First, ablation of the sympathetic renal nerves as well as chronic stimulation of baroreflex, a reflex traditionally associated with the short-term regulation only, has recently been shown to be effective treatments in drug resistant hypertension (Esler et al., 2010; Scheffers et al., 2010). Second, a number of experimental studies have revealed alterations in the brain signalling systems in animal models of hypertension (Davern and Head, 2007; Szczepanska-Sadowska, 2006; Veerasingham and Raizada, 2003). Third, several clinical studies and meta-analyses indicate comorbidity of hypertension and psychiatric disorders such as anxiety and depression (Ginty et al., 2013; Johannessen et al., 2006; Meng et al., 2012).

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http://dx.doi.org/10.1016/j.npep.2014.01.003

### 1.2. The neurogenic regulation of arterial blood pressure

The neurogenic regulation of BP may be described as a network of multiple reflex arches operating in feedback loops. The circulatory reflexes utilize information from several types of receptors such as baroreceptors and chemoreceptor. Accumulating evidence suggest that among receptors involved in the regulation of BP are the circumventricular organs (CVOs) (Ganong, 2000; Smith and Ferguson, 2010), however, their function in cardiovascular reflexes, have not yet been clarified. In order to maintain BP within an optimal range the brain cardiovascular centres process information arriving from cardiovascular receptors (Dampney, 1994) and adjust the performance of the heart, the kidneys and systemic vascular capacity via changes in the activity of the autonomic nervous system and release of hormones.

## 2. The circumventricular organs

### 2.1. Functional anatomy

The circumventricular organs (CVOs) are located in the walls of the third and the fourth ventricle of the brain ventricular system. They are distinguished from other brain regions by the lack of the blood–brain barrier (BBB), which enables their neurons to directly sense changes in the concentration of hormones and ions circulating in the bloodstream and in the cerebrospinal fluid (Cottrell and Ferguson, 2004; Ganong, 2000; Joly et al., 2007).

The blood–brain barrier is a complex structure which is formed by endothelial cells, astrocytes and pericytes. Tight junctions between the cells form a physical barrier which prevent free movements of compounds between blood and the brain (Abbott et al., 2010). The assumed function of the BBB is to maintain homeostasis of the internal environment of the brain and protect from potentially toxic compounds circulating in the bloodstream. In addition to its protective function such a barrier allows the brain neurons to utilize the same mediators which are used in the periphery, without interference between the two mediator systems. In this context, a number of compounds involved in the peripheral control of BP including angiotensin II, aldosterone, adrenaline, noradrenaline, natriuretic peptides and gaseous transmitters, have also been found to serve as neurotransmitters in the brain (Dampney, 1994; Philippu, 1988; Szczepanska-Sadowska et al., 2010; Ufnal and Sikora, 2011).

However, a complete separation from the bloodstream would make the brain unable to respond to changes in the concentration of hydrophilic compounds which do not cross the BBB. This drawback is compensated by functions of the CVOs which lack the BBB. The lack of BBB, as well as neurons which are sensitive to multiple compounds, put the CVOs in an ideal position to serve as an interface between the brain and the periphery and to operate as an integrator of hormonal and nervous regulations of animal body systems, including the circulatory system.

The most common classification of seven identified CVOs is based on their functions. The vascular organ of lamina terminalis, the subfornical organ and the area postrema are considered as the sensory organs whereas the pineal gland, the median eminence and the neurohypophysis are included into the secretory group (Cottrell and Ferguson, 2004; Duvernoy and Risold, 2007; Siso et al., 2010). There are, however, some exceptions from this straightforward classification. Namely, the vascular organ of lamina terminalis is thought to have also secretory function (Yamaguchi et al., 1993) and the pineal gland is considered as an autonomic endocrine gland which may secrete hormones independently of inputs from higher brain structures (Duvernoy et al., 2000). The seventh CVO is the subcommissural organ which functions remain obscure (Rodriguez et al., 1998). Some investigators include choroid plexuses into the group of the CVOs because of the lack of tight junctions in the endothelium, however these are vascular structures which do not possess neurons.

### 2.2. The role of the circumventricular organs in the regulation of arterial blood pressure

CVOs have multiple connections with the nucleus tractus solitarius, the rostral ventrolateral medulla oblongata, paraventricular nucleus and other brain structures which play a pivotal role in the regulation of the circulatory system (Cottrell and Ferguson, 2004; Dampney, 1994; Ganong, 2000). While the exact function of the CVOs in the control of BP is not clear, it has been shown that their neurons express receptors for a number of hormones which affect BP by peripheral mechanisms, including catecholamines, angiotensin II, vasopressin, aldosterone, natriuretic peptides and other (Cottrell and Ferguson, 2004; Ferguson and Bains, 1996; Smith and Ferguson, 2010). Furthermore, it has been found that CVOs are necessary for the development of angiotensin II-induced hypertension (Hendel and Collister, 2005) and that some of the peripherally acting hypotensive drugs may exert their therapeutic effects in part via CVOs (Collister and Hendel, 2005).

There are several approaches to evaluate biological functions of the CVOs including: intracerebroventricular (ICV) infusions, ICV infusions with concomitant peripheral infusions of hormones and/or their antagonists as well as selective infusions into a CVO or lesions of an individual CVO. Although the latter two techniques provide important information on the biological functions of a single CVO (Nobata and Takei, 2011; Osborn et al., 2012; Otsuka et al., 1986), it seems that for assessing the role of the CVOs as the links between neural and hormonal control of BP, the first two methods offer closer to real life conditions. This is because under most physiological conditions compounds which circulate in the blood and/or in the cerebrospinal fluid target all of the CVOs. Furthermore, the CVOs seem to act in redundancy (Collister and Nahey, 2009; Osborn et al., 2012; Otsuka et al., 1986) and the experimental manipulations which do not target all of the CVOs may not show the whole picture of the CVOs function in the control of BP.

It needs to be stressed, however, that the ICV infused agents may be cleared via the lymphatic system and enter the blood circulation or may penetrate behind the BBB affecting the function of peripheral tissues or deeper regions of the brain, respectively. On the other hand agents administered intravenously may be secreted via choroid plexus into the cerebrospinal fluid and act there on the CVOs. It may be assumed that the "CVOs – selectivity" as well as "peripheral – selectivity" of infused agents will be inversely correlated with the latency of the response to infusion as well as the size of a dose of infused agents.

## 3. The hemodynamic effects of intracerebroventricularly infused hormones

### 3.1. Angiotensin II

Angiotensin II (Ang II) is a peptide which contributes to the regulation of BP by multiple mechanisms including vasoconstriction, secretion of aldosterone and vasopressin, modulation of sympathetic nervous system activity, control of thirst and sodium appetite. All of these actions are mediated by stimulation of angiotensin II type 1 (AT1) receptor and lead to an increase in BP. Stimulation of AT2 receptors seem to evoke the opposite effects, however the importance of AT2 receptors in the regulation of BP remains to be fully understood (Crowley and Coffman, 2012).