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Review Article

Involvement of Cerebellar Adrenomedullin in Cardiovascular Regulation and Vasopressor Response to Acute Stress

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Abstract

Adrenomedullin (AM) is a peptide involved in cardiovascular regulation. AM exerts numerous biological activities through the activation of AM1 and AM2 receptors. AM immunoreactivity, AM binding sites and CRLR, RAMP1, RAMP2 and RAMP3 are expressed in rat cerebellum vermis. There is a dysregulation of cerebellar AM system during hypertension since it was shown an up-regulation of cerebellar CGRP1 and AM2 receptors and a down-regulation of AM1 receptor associated with a decreased AM expression. We anticipated a possible functional role of cerebellar AM on blood pressure regulation. Indeed, *in vivo* microinjection of AM into the cerebellar vermis caused a profound hypotensive effect in Spontaneously Hypertensive Rats (SHR) but not in normotensive Wistar Kyoto (WKY) rats, this through AM1 receptor stimulation. The role of the cerebellum in the cardiovascular response to stress is elusive. We evaluated the functional role of AM during acute stress. AM was administered into the cerebellar vermis of normotensive WKY and *Sprague Dawley* (SD) rats and SHR subjected to footshock, an acute stress which causes sympathoadrenal activation with increases in arterial blood pressure and heart rate. We show that AM (0.2 and 200 pmol) microinjection into the cerebellar vermis in SD, WKY and SHR rats decreases vasopressor response induced by footshock, suggesting the involvement of sympathetic outflow. Taken together, our results demonstrate a role for cerebellar AM in the regulation of arterial blood pressure and in the cardiovascular response to stress. Likewise, they constitute a novel mechanism of blood pressure control which has not been described so far.

Keywords: Adrenomedullin; Hypertension; Acute Stress; Cerebellum; Vermis

Abbreviations

AC: Adenylyl Cyclase; ACTH: Adrenocorticotropic Hormone; AM: Adrenomedullin; AM1 receptors: AM type 1 receptors; AM2 receptors: AM type 2 receptors; AUC: Area Under the Curve; ANG II: Angiotensin II; cAMP: 3',5' cyclic adenosine monophosphate; cGMP: Cyclic Guanosine Monophosphate; CGRP: Calcitonin Gene-related Peptide; CNS: Central Nervous System; CRH: Corticotropin Releasing Hormone; CRLR: Calcitonin Receptor-Like Receptor; ERK: Extracellular Regulated Kinases; FS: Footshock; GABA: Gamma-Aminobutyric Acid; GPCR: G Protein Coupled Receptor; HPA: Hypothalamic-Pituitary-adrenal Axis; ICV: *Intracerebroventricular*; MAP: Mean Arterial Pressure; NO: Nitric Oxide; NTS: Nucleus Tractus Solitari; PKA: Protein Kinase A; PVN: Paraventricular Nucleus; RAMPs: Receptor Activity-Modifying Proteins; ROS: Reactive Oxygen Species; RVLM: Rostral Ventrolateral Medulla; SAP: Systolic Arterial Pressure; SHR: Spontaneously Hypertensive Rat; SON: Supraoptic Nucleus; VLM: Ventrolateral Medulla; WKY: Wistar Kyoto Rat

Introduction

Cardiovascular regulation is complex and involves different peptides and brain structures including the cerebellum. There is little information about the role of the cerebellum in cardiovascular regulation, but it has been shown that stimulation of several cerebellar regions produces changes in arterial blood pressure and heart rate [1-3]. Effectively, in anesthetized rabbits electric stimulation of anterior vermis, medial cortical regions of lobules I, II and III, posterior vermis (lobules VII and VII) and uvula (Lobule IX) induces bradycardia, blood pressure fall and transient inhibition of sympathetic renal activity [1,4-6], and stimulation of the posterior vermis causes a cardiovascular response characterized by hypotension and bradycardia [5]. On the contrary, electric stimulation of the rostral region of fastigial nucleus in anesthetized rabbits produces a pressor response [7]. Anatomical evidence supports the role of fastigial nucleus in cardiovascular function and in autonomic nervous system regulation. This nucleus receives inputs from vestibular structures and from cerebellar Purkinje cells, which mediate vestibular and other afferent signals necessary for blood pressure compensation [2]. Indeed, it has been identified various cardiovascular modules, such as fastigial nucleus, anterior vermis, posterior vermis, uvula (lobe IX), nodulus (lobe X), as stimulation of these structures involves changes in blood pressure, respiratory rate and vascular resistance [1].

Within the peptides involved in cardiovascular regulation, Adrenomedullin (AM) is considered a multifunctional peptide which

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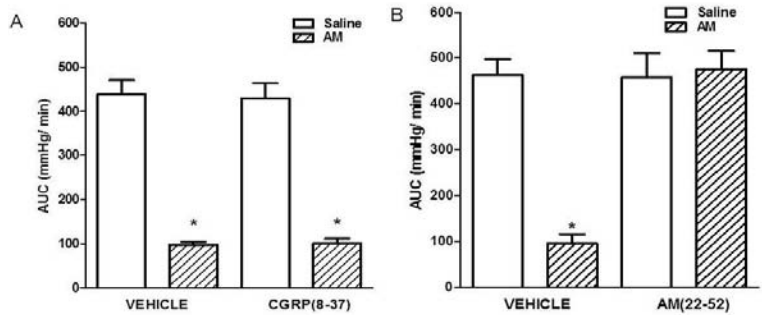

Figure 1: Effect of AM *in situ* administration into cerebellar vermis of SHR rats**.** Effect of CGRP (8-37) (Panel A) and AM (22-52) (Panel B) on the time course of changes in Systolic Arterial Pressure (SAP) induced by microinjection of AM. SHR rats were microinjected into the vermis with saline (5µL), AM (200 pmol/5µL), AM (22-52) (200pmol/5µL), AM+AM (22-52), CGRP (8-37) (200 pmol/5µL) and AM+CGRP (8-37). Results are expressed as mean ± S.E.M. of Area Under the Curve (AUC) of SAP (n=8). *p<0.05 vs. its own control.

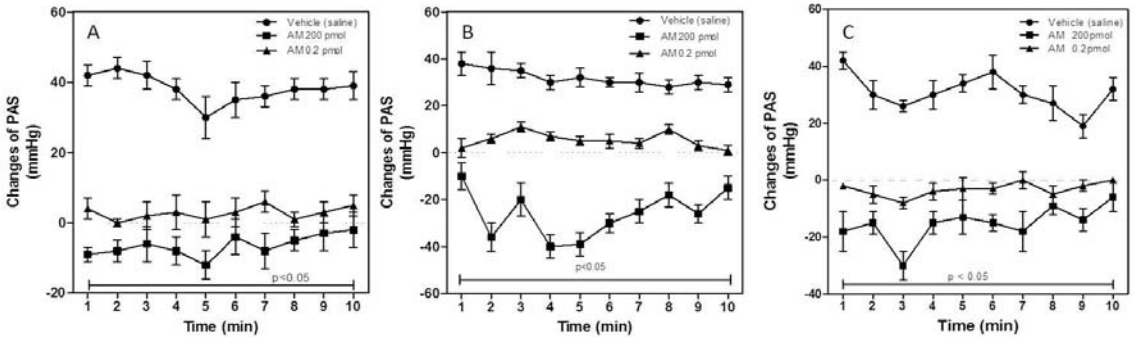

Figure 2: Effect of AM *in situ* administration into cerebellar vermis of SD, WKY and SHR rats subjected to Foot Shock (FS) stress. SD (Panel A), WKY (Panel B) or SHR (Panel C) rats were microinjected into the vermis with vehicle (5µL) or AM (0.2 or 200 pmol/5µL) and then subjected to acute stress. Results are expressed as mean ± S.E.M. of Area Under the Curve (AUC) of Systolic Arterial Pressure (SAP). (n=10). *p<0.05 vs. vehicle. #p<0.05 vs. AM 0.2 pmol/5µL.

exerts numerous biological activities through the activation of two specific receptors, the AM type 1 (AM1) and type2 (AM2) receptors [8,9], formed from the obligate co-expression of a class-B, G Protein Coupled Receptor (GPCR), the Calcitonin Receptor-Like Receptor (CRLR) and Receptor Activity-Modifying Proteins (RAMPs) 2 or 3, respectively [9-11]. The Calcitonin Gene-Related Peptide 1 (CGRP1) receptor is formed of a complex between CRLR and RAMP1 [10].

Specifically in the cerebellum it was detected AM immunoreactivity, AM binding sites and CRLR, RAMP1, RAMP2 and RAMP3 expression [12-15]. In effect, AM immunoreactivity was localized in the lateral, interpositus and medial nuclei; in granule of the cerebellar cortex, the molecular layer, Purkinje cells, Golgi neurons, and mossy terminal nerve fibers in the granular as well as neurons of the cerebellar nuclei [12,16]. In addition, it has been shown the presence of RAMP1 and RAMP2 mRNA in Purkinje cells and RAMP3 mRNA in cerebellar granular cells [17]. Likewise, CRLR and RAMP1 were detected on the surface of the Purkinje cell bodies and in their processes [18,19]. In the cerebellum, activation of AM receptors are associated to several signaling pathways such as Adenylyl Cyclase/ cyclic Adenosine Monophosphate (AC/cAMP), cyclic Guanosine Monophosphate/ Nitric Oxide (cGMP/NO), extracellular regulated kinases (ERK1/2) and regulation of reactive oxygen species (ROS) metabolism, indicating the existence of a local functional cerebellar adrenomedullinergic system [20-27].

Recently we have shown that hypertension dysregulates AM cerebellar system. In effect, we demonstrated an up-regulation of cerebellar CGRP1 (CRLR+RAMP1) and AM2 (CRLR+RAMP3) receptors, concomitantly with a down-regulation of AM and AM1 receptor (CRLR+RAMP2) during hypertension [25], as cerebellar vermis CRLR, RAMP1 and RAMP3 expression was increased significantly while RAMP2 was reduced in Spontaneously Hypertensive Rats (SHR) compared with Wistar Kyoto (WKY) rats. The reduction in cerebellar vermis AM expression of SHR rats could be responsible for the up-regulation of AM2 receptors and binding sites observed by autoradiography [28].

The evidence suggests that CRLR/RAMP2 complex represents the main receptor involved in the biological actions of the AM. Therefore, RAMP2 is mainly expressed in the basal state while RAMP3 expression remains relatively low. In pathological conditions such as hypertension, there are changes of RAMPs expression, specifically a switch from RAMP2 to RAMP3 [25,29]. Therefore, decreased RAMP2 and AM expression suggests that these changes may constitute a mechanism which contributes to the development of genetic hypertension, and support the notion that this peptide is involved in the regulation of blood pressure in cerebellum. Furthermore, up-regulation of CRLR, RAMP1 and RAMP3 expression would promote the interaction of AM with CGRP1 and AM2 receptors, rather than with AM1 receptors, thereby favoring the compensatory mechanism to increased blood pressure. Alternatively, these changes could be the initial disturbance that would result in dysregulation of the mechanisms controlling blood pressure, since these changes

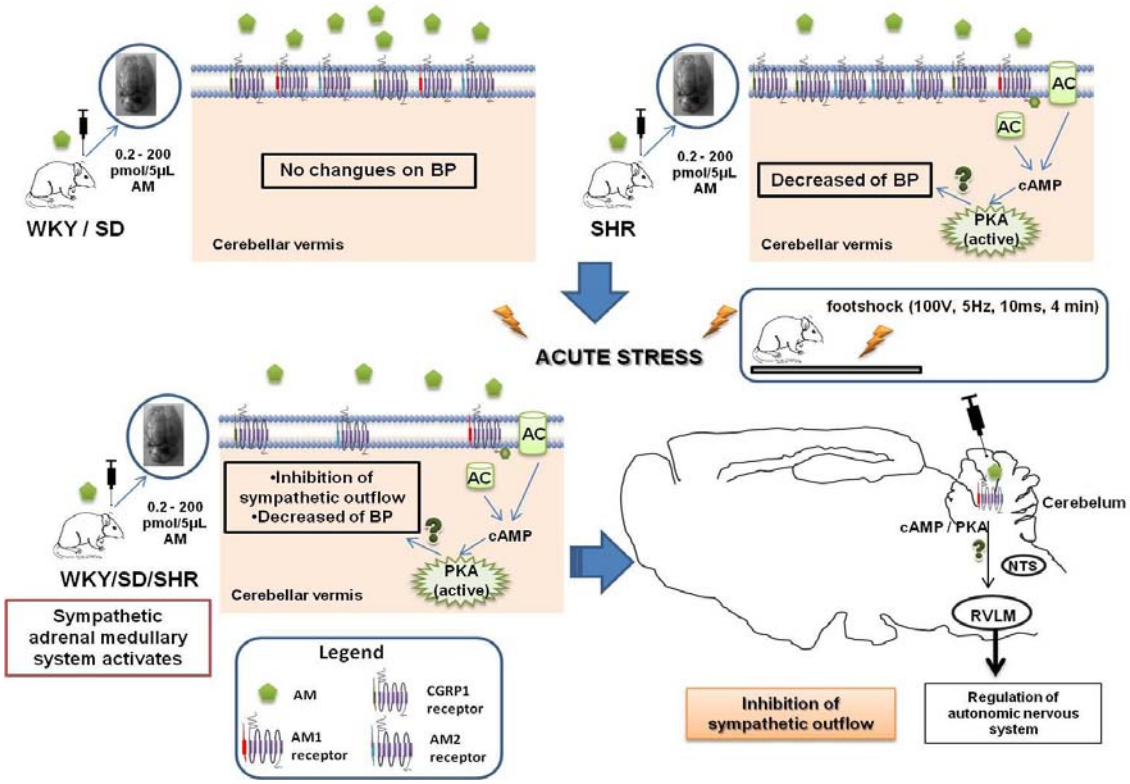

Figure 3: Proposed model of effect of AM microinjection into the cerebellar vermis on blood pressure regulation during normotension, hypertension and acute stress. The expression of AM and its receptor components, CRLR, RAMP1, RAMP2, and RAMP3 are altered in SHR when compared to WKY rats: In hypertensive rats, AM and RAMP2 expression is reduced, while RAMP1, RAMP3, and CRLR expression is significantly increased. Microinjection of AM (0.2 - 200 pmol/5µL) into the cerebellar vermis of SHR rats causes a powerful and significant hypotensive response, which is specific and dose-dependent via AM1 receptors possibly mediated by AC/cAMPc/PKA. This hypotensive effect is manifested only during hypertension. Microinjection of AM (0.2 - 200 pmol) *in situ* into the cerebellar vermis in SD, WKY and SHR rats, significantly decreased the vasopressor response induced by footshock stress (100V, 5 Hz, 10 msec, for 4 minutes), suggesting that the hypotensive action is mediated through regulation of sympathetic outflow possibly by cerebellum – RVLM connection. AC: Adenylyl cyclase, BP: Blood pressure, PKA: Protein kinase A, SD: Sprague Dawley rats, SHR: Spontaneously hypertensive rats, WKY: Wistar Kyoto Rats.

are present from the early stages of life of hypertensive rats [25]. In fact, lowering blood pressure with an oral antihypertensive drug like valsartan during eleven days, reduced blood pressure and reversed AM and its receptor components expression to those levels found in normotensive rats [30], suggesting that hypertension induces adaptive changes to compensate a rise of blood pressure.

Physiological Effects of Cerebellar AM

Little is known about the functional role of AM in cerebellum. Nevertheless, we showed that microinjection of AM into the cerebellar vermis of hypertensive rats causes a powerful and significant hypotensive response, which is specific and dose-dependent (0.02 to 200 pmol/5µL) [25]. The specificity of the hypotensive action of AM administered into the cerebellar vermis of SHR rats is based on the fact that microinjection of the peptide outside the vermis did not cause the hypotensive effects, and *in situ* administration of a pressor peptide such as angiotensin II (ANG II) or vehicle into cerebellar vermis increased Median Arterial Pressure (MAP) in similar magnitude in both WKY and SHR rats. In addition, it was shown that AM's actions in the cerebellar vermis in SHR rats are mediated through AM1 receptor, as AM receptor specific antagonist, AM(22-52) (200 pmol/5µL), co-injected with AM (200 pmol/5µL) blunted AM's hypotensive effect, while CGRP(8-37) (200 pmol/5µL) had no effect on AM actions [25,26] as seen in Figure 1, which shows the effect of AM on Area Under the Curve (AUC) of Systolic Arterial Pressure (SAP). These results provide the first functional evidence *in vivo* of a role for AM in the cerebellar vermis in the control of blood pressure. This hypotensive effect is manifested only during hypertension since in WKY rats, administration of vehicle or AM (200 pmol/5µL) into cerebellar vermis increased MAP in similar magnitude. The possible cause of the differences in the AM action among normotensive and hypertensive rats may be variable and has been described for other brain structures, since the infusion of AM reduces blood pressure in both normotensive and hypertensive rats in a dose dependent manner; however the fall in blood pressure was higher in hypertensive rats compared to the normotensive [31]. Similarly, it was reported that Rostral Ventrolateral Medulla (RVLM) neurons of SHR rats are more sensitive and have an increased response to ANG II with respect to the WKY [32]. Therefore, the hypotensive effect induced by the intracerebellar administration of AM in SHR could be due to an increase in sensitivity and response in SHR compared with WKY rats. Alternatively, this differential response may be the manifestation of the cerebellar dysregulation of signaling pathways, or AM and AM1 receptor expression which are reduced during hypertension [20,25,26]. The possible mechanism of cerebellar AM-induced hypotensive action in SHR rats has not

been established so far, but could be associated with the regulation of sympathetic efflux and possibly requires a stimulated system.

Effects of Cerebellar AM on Acute Stress

Stress is defined as a state in which homeostasis is actually threatened or perceived to be so; homeostasis is reestablished by a complex repertoire of behavioral and physiological adaptive responses of the organism. In fact, all living organisms maintain a complex dynamic equilibrium, or homeostasis, which is constantly challenged by internal or external adverse effects, termed stressors [33]. The response to environmental stressors and adverse forces involve the activation of complex pathways in the Central Nervous System (CNS), ranging from the perception of stress to behavioral, autonomic and endocrine responses, and the increase in activities of several physiological systems that induce the interruption of homeostasis [34,35].

The central control stations of the stress system are located in the hypothalamus and brain stem and include parvocellular neurons that synthesize and secrete the Corticotropin Releasing Hormone (CRH), neurons of the paraventricular nucleus of the hypothalamus releasing arginine-vasopressin and the Locus Coeruleus (LC) considered the central sympathetic system [36,37]. The Hypothalamic-pituitary-adrenal Axis (HPA), together with the sympathetic adrenomedullary efferent system, represents the effector organ, which through brain stimulation influence all body organs on exposure to a stressor stimulus [38]. In the brain there is also modulation of the vagal efferent and the sacral portion parasympathetic efferent that mediate gut responses to stress [39].

Stress represents a critical influence on motor system function and has been shown to impair movement performance. The role of the cerebellum in the response to stress is elusive. In this regard, the evidence show that exposure to two weeks of mild restraint stress causes lasting impairments in skilled movement and balance in rats associated with an altered expression of 39 genes and nine micro RNA (miRNAs) in the cerebellum, a structure known to contribute to the learning and coordination of skilled movement [40]. Likewise, in rats exposed to stress by forced swimming for seven days, the cerebellum shows a significant increase in lipid peroxidation, suggesting that stress activates processes of free radical production leading to an increase of lipid peroxidation [41].

Some neuroendocrine factors such as catecholamines, CRH, serotonin, endothelins, vasopressin and ANG II act in the central circuits, mediating stress responses [38]. The involvement of AM in the stress response is poorly understood. In this regard, it has been shown that movement restriction stress stimulates sympathetic activity and the HPA axis, and produces a significant increase in AM plasma levels, and in pituitary and adrenal glands [42]. This suggests a regulatory and protective function for AM to counter the HPA axis activation induced by a variety of physiological and psychological stressors [42]. Effectively, AM endocrine effects are mediated through the inhibition of Adrenocorticotropic Hormone (ACTH), cortisol [43], corticosterone [44] and ANG II-stimulated aldosterone release [45].

Several of AM protective actions during stress could be mediated through the CNS. The evidence supports this possibility, since the existence of AM receptors and their components in brain structures and specifically in the cerebellum has been demonstrated [12,20]. Likewise, our recent findings demonstrate the existence of a functional cerebellar adrenomedullinergic system, which is dysregulated during hypertension [20,25]. Moreover, AM administration into the cerebellar vermis during hypertension produces a profound hypotensive effect, which is dose-dependent and site-specific, and is mediated through AM1 receptor stimulation [25]. Although these findings demonstrate that cerebellar AM is involved in the regulation of blood pressure, it is not clear whether the cerebellar adrenomedullinergic system is able to regulate the cardiovascular response to stress. The evidence indicates that cerebellar AM action could be associated with the regulation of sympathetic activity and seems to require a stimulated system. If this is the case, AM administration into the cerebellar vermis should counteract the vasopressor response produced by Footshock (FS), an acute stress which causes sympathoadrenal activation with increases in arterial pressure and heart rate, plasma catecholamines and blood sugar, and decreases intestinal motility [46]. Our results points toward this possibility as acute stress produced by FS significantly increased blood pressure in SD, SHR and WKY rats [47], possibly due to an increment in the release of catecholamines into the circulation [48-50], and microinjection of AM (0.2 pmol/5μL) into the cerebellar vermis blunted vasopressor response to FS in normotensive and hypertensive rats, suggesting that intracerebellar AM may act by inhibiting sympathetic efflux. Moreover, in rats subjected to FS, intracerebellar administration of a higher dose of AM (200 pmol/5μL) not only inhibited the vasopressor response to FS, but also produced a profound and significant hypotensive response (Figure 2). This AM inhibitory effect was dose-dependent and site-specific, as *in situ* AM administration outside the cerebellar vermis was unable to alter the vasopressor response induced by the FS. Furthermore, AM effect was specific since the administration of ANG II, a pressor peptide, into the cerebellar vermis did not alter vasopressor response to acute stress induced by FS when compared to vehicle [47] even though it was demonstrated the presence of ANG II receptors in the cerebellum [51,52]. In this sense, it was shown that iontophoretic application of ANG II in the cerebellum causes depression of the Purkinje cells firing rate [53]. These results constitute the first *in vivo* functional evidence of the role of cerebellar AM in the control of blood pressure response during stress.

AM hypotensive and inhibitory effect on the sympathoadrenal response to FS stress is difficult to explain. In this respect we could speculate that the cerebellum, through its neuroanatomic connections from the fastigial nucleus and mediated via NO/cGMP signaling pathway exerts a powerful counter-regulatory action on the excitatory brain nuclei which participate in blood pressure regulation. It is known that the fastigial nucleus plays an important role in the regulation of the autonomic nervous system, since this nucleus projects to brain stem structures such as the RVLM, which in turn receives innervation from the hypothalamic Supraoptic Nucleus (SON) and Paraventricular Nucleus (PVN). In addition, NO neurons are found in autonomic centers including PVN, SON, Nucleus Tractus Solitari (NTS) and Ventrolateral (VLM) and medial-lateral medulla [54]. In PVN, NO inhibits sympathetic activity through the stimulation of Gamma-Aminobutyric Acid (GABA) ergic interneurons [55,56]. On the other hand, in NTS and VLM, NO has both sympatho-excitatory and sympatho-inhibitory effects,

suggesting that in the brain stem, NO regulates sympathetic efflux, through a balance of the outputs of these autonomic centers [54]. Moreover, AM *Intracerebroventricular* (ICV) injection stimulates hypothalamic NO production and activates NO-producing neurons in the PVN [57]. The stimulation of sympathetic efflux by AM-ICV administration together with inhibition of sympathetic efflux by NO in PVN suggests that AM-induced stimulation of hypothalamic nitrergic system may be part of a feedback mechanism, which acts to restore the homeostatic balance [58]. In support of this, low doses of AM-ICV administration have been reported to cause inhibition of renal sympathetic activity [59]. Additionally, Fujita et al. [60] found that endogenous brain AM inhibits sympathetic activation through its antioxidant action. On the other hand, Xu and Krukoff [61] indicated that AM in RVLM exerts an inhibitory effect on baroreflex activity through a mechanism mediated by specific AM receptors, where activation of Protein Kinase A (PKA) is involved.

Contrary to the AM inhibitory effect in cerebellum, there is evidence indicating that AM in other several brain regions increases sympathetic activity and renal sympathetic efflux. Indeed, AM administration in the RVLM increases blood pressure, suggesting AM stimulation of RVLM neurons which control cardiac sympathetic activity [62,63]. In addition, AM-ICV administration caused an increase in blood pressure, which seems to be mediated by increased sympathetic activity [64-66] as it was blocked by peripheral administration of an alpha-adrenergic blocker phentolamine. This data support the notion that AM is involved in the central regulation of cardiovascular and sympathetic renal function. Similarly, Taylor et al. [57] found that AM-ICV administration increases plasma corticosterone levels, suggesting that AM acts within the hypothalamus stimulating the release of CRH, and thus increasing HPA axis activity. Moreover, AM-ICV administration stimulates sympathetic efflux and renal and abdominal sympathetic discharge [66-69] and increases baroreflex sensitivity [67]. In addition, AM-ICV administration activates PVN, which is associated with central cardiovascular and sympathetic regulation [66,68]. Also, AM microinjection stimulates tyrosine hydroxylase gene expression, known as rate-limiting enzyme of catecholamine biosynthesis in the LC [66]; were noradrenergic neurons participates in important processes regulating cardiovascular function. Thus it is possible that AM mediates some of its effects through its actions on LC catecholaminergic system [66,69].

Conclusion

The evidence indicates that cerebellar AM constitutes a powerful hypotensive peptide during hypertension and reinforces the novel concept of the existence of a cerebellar adrenomedullinergic system of physiological importance. Its protective role against acute stress through the inhibition of sympathetic efflux predicts a potential future in its pharmacological use. Thus, the study of the neuroanatomical and neuropeptidergic pathways involved in cerebellar AM actions on blood pressure regulation and the cardiovascular response to acute stress is an open matter Figure 3.

Acknowledgements

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