symmetry

MDPI

Article

Blood Pressure Correlates Asymmetrically with Neuropeptidase Activities of the Left and Right Frontal Cortices

Ana Belén Segarra [1,†], Isabel Prieto [1,†], Inmaculada Banegas [1], Magdalena Martínez-Cañamero [1], Marc de Gasparo [2] and Manuel Ramírez-Sánchez [1,*]

[1] Department of Health Sciences, University of Jaén, 23071 Jaén, Spain; asegarra@ujaen.es (A.B.S.); iprieto@ujaen.es (I.P.); ibanegas@ujaen.es (I.B.); canamero@ujaen.es (M.M.-C.)
[2] Cardiovascular & Metabolic Syndrome Adviser, Rue es Planches 5, 2842 Rossemaison, Switzerland; m.de_gasparo@bluewin.ch
* Correspondence: msanchez@ujaen.es
† These authors have contributed equally to this work.

Abstract: It was suggested that the brain-heart connection is asymmetrically organized. However, evidence connecting neurochemical factors from each brain hemisphere with changes in cardio-vascular functions have not yet been reported. In order to analyze potential asymmetrical connections between brain neurochemical factors with cardio-vascular functions, we studied the level of correlations between the left and right frontal cortex (FC) soluble (Sol) and membrane-bound (MB) neuropeptide-degrading enzymes alanyl (AlaAP), cystinyl (CysAP), and glutamyl (GluAP) aminopeptidase activities, involved among others in the metabolism of angiotensins, with heart rate (HR), systolic (SBP), and diastolic (DBP) blood pressure, in rats treated or not with hypotensive or hypertensive drugs such as captopril, propranolol or L-NAME. The present study suggests the existence of a bidirectional asymmetrical connection between these brain neuropeptidases and cardio-vascular functions. Specifically, depending on treatment, in control group, Sol AlaAP from the left FC correlates negatively with SBP and DBP. In captopril-treated animals, MB CysAP and MB GluAP from the right FC correlate negatively with HR. In L-NAME treated rats, Sol CysAP from the right FC correlates negatively with DBP. No significant correlations were observed in the propranolol group. Considering together all the values obtained from the left or the right cortex of the four groups regardless of drug treatment, the results demonstrated significant negative correlations between these neuropeptidase activities, mainly from the left frontal cortex, with the levels of systolic and diastolic blood pressure. Remarkably, these findings contrast drastically with previously reported results indicating significant positive correlations between the left frontal cortex with other peripheral functions such as water intake and diuresis. Both results represent noteworthy information that strongly supports the concept of a bidirectional asymmetric organization of neurovisceral integration involving left and right brain neurochemical processes with peripheral physiological functions, most probably mediated by the autonomic nervous system. Overall, the present results suggest that cognitive functions involving the frontal cortex may be asymmetrically connected with peripheral physiological processes, and vice versa.

Keywords: brain asymmetry; cardio-vascular function; neuropeptidases; systolic blood pressure; diastolic blood pressure; neurovisceral integration

Citation: Segarra, A.B.; Prieto, I.; Banegas, I.; Martínez-Cañamero, M.; de Gasparo, M.; Ramírez-Sánchez, M. Blood Pressure Correlates Asymmetrically with Neuropeptidase Activities of the Left and Right Frontal Cortices. *Symmetry* **2021**, *13*, 105. https://doi.org/10.3390/sym13010105

Received: 15 December 2020
Accepted: 7 January 2021
Published: 8 January 2021

1. Introduction

The brain-heart connection is under growing interest because of the clinical potential of a two-way relationship between cognitive functions and cardiac dynamic, such as heart rate variability, and vice versa [1]. A functional connection involving the renin-angiotensin aldosterone system (RAAS) was suggested when the relationship between brain and cardiac angiotensinase activities were analyzed under vasoactive drug treatments [2]. Subsequent studies suggested that these chemical brain-heart interactions could

be asymmetrically organized [3]. In addition, significant correlations were reported between brain and peripheral physiological processes such as water intake, diuresis or water balance values [4]. However, conclusive data that asymmetrically linked neurochemical factors (i.e., neuropeptidases/angiotensinases) from the left or right hemispheres (and consequently the functions they regulate on each side) with cardio-vascular functions, such as heart rate (HR), systolic (SBP) or diastolic blood pressure (DBP), and vice versa, have not yet been provided.

The frontal cortex is not only implicated in the control of cognitive functions but it is also important in the neuroendocrine and autonomic control of cardio-vascular processes [5]. For example, the left frontal cortex has been associated with communicative functions, focused attention or parasympathetic control whereas the right frontal cortex was related to spatial performance, stress response and sympathetic control [6,7]. In addition, changes in bilateral activity, such as the predominance of intra- or inter-hemispheric interactions, are closely related to the modulation of emotional processes [8]. However, evidence regarding asymmetrical connections between some brain neuropeptidase activities, such as angiotensinases, involved in the modulation of emotional processes, and cardio-vascular functions are required. Therefore, our objective was to analyze the possible correlations between the neuropeptide-degrading enzymes alanyl (AlaAP, EC 3.4.11.2), cystinyl (CysAP, EC 3.4.11.3), and glutamyl aminopeptidase (GluAP, EC 3.4.11.7) activities, in their soluble (Sol) and membrane-bound (MB) forms, obtained from the left or right frontal cortex, with HR, SBP, and DBP in rats treated or not (controls, CT) with the hypotensive drugs captopril (CA) and propranolol (PR), or the hypertensive one L-nitro-arginine methyl ester (L-NAME, LN). In addition, in order to obtain a general perspective of the global left or right behavior, a correlational study was also performed regardless of the drug treatments. The functional status of their corresponding substrates is the result of the activity of these enzymes. They hydrolyze respectively angiotensin III and enkephalins (AlaAP), oxytocin and vasopressin (CysAP) and angiotensin II (GluAP) [9]. These neuropeptides have been reported to be anxiolytic (enkephalins and oxytocin) or anxiogenic (angiotensin II) agents. In addition, CysAP has been identified as the insulin-regulated aminopeptidase (IRAP) and also as the AT4 receptor which binds Ang IV with high affinity [10]. Therefore, CysAP activity may be involved in cognitive and cardiovascular functions and also in glucose uptake through its functional connection with the GLUT4 transporter [9]. The present research was conducted to study the bilateral behavior of these aminopeptidase activities (AlaAP, CysAP, GluAP) in the left and right frontal cortex, in relation to parameters of the cardiac dynamic such as SBP, DBP, and HR.

2. Materials and Methods

Thirty-two adult male Wistar rats, weighing 100–150 g at the start of the research, were used in this investigation. The animals were separated at random in controls (CT, n = 8), captopril-(CA, n = 8,), propranolol-(PR, n = 8) and L-NAME-treated (LN, n = 8). CA (100 mg/kg/day), PR (100 mg/kg/day) and LN (70 mg/kg/day) were added to the drinking water during four weeks. The way of administration, period of treatment and dosage, were previously reported as suitable to reach the complete action of the drugs [11,12]. To avoid cyclic variations, the research was performed in summer, under environmental light/dark conditions, being light between 9:00 a.m. and 12:00 noon [13]. The study was carried out according to the European Communities Council Directive 86/609/EEC and was approved by the bioethics committee of the University of Jaén. HR, SBP, and DBP were determined using tail-cuff plethysmography in unanaesthetised rats at reception for initial values and at the end of the experiments for final values. After four weeks of treatments and after the final determinations of the cardiovascular parameters, the rats were anaesthesized with equithensin [14], perfused with saline, then each brain quickly removed. The left and right frontal cortices were obtained in accordance to the stereotaxic Paxinos and Watson atlas [15]. The chosen tissue was between the anterior borders of the left and right frontal lobes up to 13.2 mm anterior to the interaural line. Briefly, in order to

obtain the soluble fraction, the left or right frontal cortices were homogenized separately in a hypoosmolar medium (10 mmol/L HCl-Tris buffer, pH 7.4) and ultracentrifuged at 100,000× *g* for 30 min at 4 °C. The resulting supernatants were used for Sol protein and enzyme determinations. To obtain the membrane-bound fraction, the pellets were re-homogenised in an HCl-Tris buffer (pH 7.4) and 1% Triton X-100 to solubilize membrane proteins. After centrifugation (100,000× *g*, 30 min, 4 °C), the level of proteins and the MB aminopeptidase activities were analyzed in triplicate in the supernatants. The activities of Sol and MB AlaAP, CysAP, and GluAP were measured fluorometrically using the arylamide derivatives, glutamyl-, alanyl-, and cystinyl-β-naphthylamide, as substrates as previously described in detail [14]. GluAP was determined using Glu-β-naphthylamide as a substrate: 10 mL of each supernatant was incubated for 120 min at 37 °C with 1 mL of the substrate solution (2.72 mg/100 mL Glu-β-naphthylamide, 10 mg/100 mL bovine serum albumin, 10 mg/100 mL dithiothreitol (DTT), and 0.555 g/100 mL $CaCl_2$ in 50 mmol/L HCl-Tris, pH 7.4). AlaAP and CysAP were measured using Ala or Cys-β-naphthylamide as substrates, such that 10 mL of each supernatant were incubated for 30 min at 25 °C with 1 mL of the substrate solution, that is 2.14 mg/100 mL of Ala-β-naphthylamide or 5.53 mg/100 mL of Cys-β-naphthylamide, 10 mg/100 mL bovine serum albumin, and 10 mg/100 mL DTT in 50 mmol/L of phosphate buffer (pH 7.4 for AlaAP) and 50 mmol/L HCl-Tris buffer (pH 6 for CysAP). The reactions were stopped by adding 1 ml of 0.1 mol/L of acetate buffer, pH 4.2. The quantity of β-naphthylamine released as a result of the enzymatic activity was assayed fluorometrically at a 412 nm emission wavelength with an excitation wavelength of 345 nm. Proteins were measured in triplicate with bovine serum albumin as a standard. Specific Sol or MB aminopeptidase activities were expressed as pmol of the corresponding substrate hydrolyzed per minute per milligram of protein. Fluorogenic assays were linear with respect to time of hydrolysis and protein content. The statistical differences between groups were calculated using a two-way analysis of variance. Post hoc comparisons were performed via LSD tests. To analyze the possible connection between the enzymatic activities of the left and right frontal cortex with parameters of the cardiac dynamics, the Pearson's coefficients of correlation were calculated. The calculations were carried out using SPSS 13.0 and STATA 9.0 (STATA Corp, College Station, TX, USA). p values less than 0.05 were considered as significant.

3. Results

The SBP values after four weeks treatment were previously reported [8]. In comparison with the values at reception, the final values of SBP increased significantly ($p < 0.001$) in untreated controls and L-NAME treated rats. DBP increased ($p < 0.001$) only in the LN group and HR did not change. Taking together the data of treated and untreated rats (n = 32), SBP ($p < 0.001$) and DBP ($p < 0.01$) increased significantly while HR did not change between the initial and final values (Figure 1). Considering the final values, the LN group had higher ($p < 0.001$) SBP and DBP values than CT, CA and PR groups. In contrast, the LN group had lower HR values than CA ($p < 0.05$) and PR ($p < 0.01$) (Figure 2).

The mean levels of the enzymatic activities from the left and right frontal cortex (used for the present analysis) were also previously reported [8]. Briefly, Sol GluAP was higher in the left FC than in the right one in all groups except in L-NAME treated rats in which there was no left vs. right differences. In contrast, there was a right predominance for MB GluAP in the LN group without left vs. right differences in the other groups. No differences between left and right FC were observed for Sol AlaAP in any of the groups studied, but there was a clear left predominance in the CAP group for MB AlaAP. While only control WKY demonstrated an asymmetry of right prevalence for Sol CysAP, all the treated groups exhibited a left predominance for MB CysAP.

Depending on the treatment, the present results demonstrate specific individual correlations between neuropeptidase activities from the left or right FC versus cardiovascular parameters. In controls, Sol AlaAP from the left FC correlates negatively with SBP ($r = -0.763$, $p = 0.02$) and DBP ($r = -0.797$, $p = 0.01$). In captopril-treated animals,

MB CysAP (r = −0.713, p = 0.04) and MB GluAP (r = −0.763, p = 0.02) from the right FC, correlate negatively with HR. In L-NAME treated rats, Sol CysAP from the right FC correlates negatively (r = −0.720, p = 0.04) with DBP. No significant correlations were observed in the PR group (Figure 3).

In order to obtain a broader perspective of the study, we performed an analysis considering together all the values obtained from the left or the right cortex of the four groups regardless of drug treatment. For each enzymatic activity, if we consider together the left FC data (n = 32) or the right FC data (n = 32) of the four treated and untreated groups, all the activities from the left side correlate significantly and negatively with SBP and DBP. Only Sol and MB CysAP from the right FC correlate significantly, but negatively with SBP and DBP. No correlations regardless treatments were observed with HR (Figure 4).

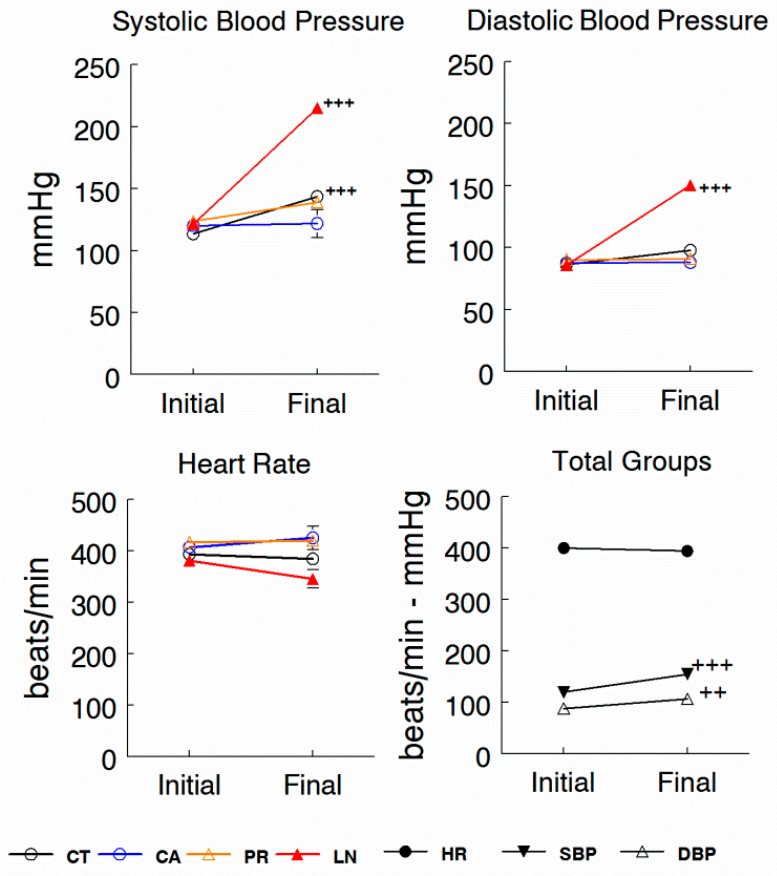

Figure 1. Initial and final heart rate, systolic and diastolic blood pressure values in controls and after 4 weeks vasoactive drug treatments. Mean ± SEM levels for initial and final values of systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), and heart rate (HR, beats/min) in control-(CT, black lines and open black circles), captopril-(CA, blue lines and open blue circles), propranolol-(PR, rose lines and open rose triangles) and L-NAME-(LN, red lines and close red triangles) treated rats. The figure for total groups indicates the initial and final values of HR (n = 32), SBP (n = 32) and DBP (n = 32) taking together all the data of the four groups independently of the treatment. (+) indicates the level of significance for comparisons with initial values. Double sign (p < 0.01); triple sign (p < 0.001).

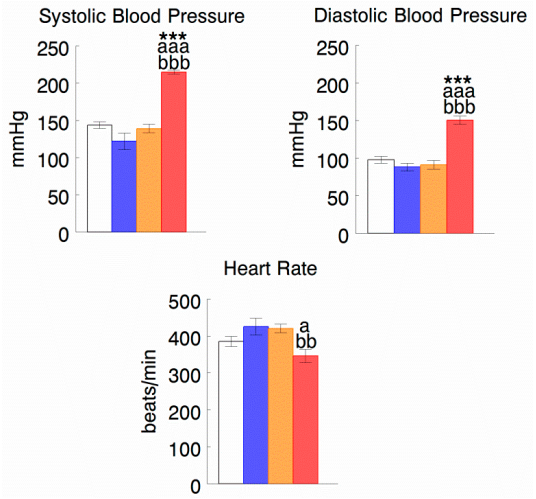

Figure 2. Bar's diagrams representing the mean ± SEM levels for final values of control-(open bars), captopril-(blue bars), propranolol-(rose bars) and L-NAME-(red bars) treated rats. They illustrate the comparisons between the final values after four weeks of treatment of the three treated and untreated groups. (*) comparison with CT, (a) comparison with CA, (b) comparison with PR. Single sign or letter ($p < 0.05$); double sign or letter ($p < 0.01$); triple sign or letter ($p < 0.001$).

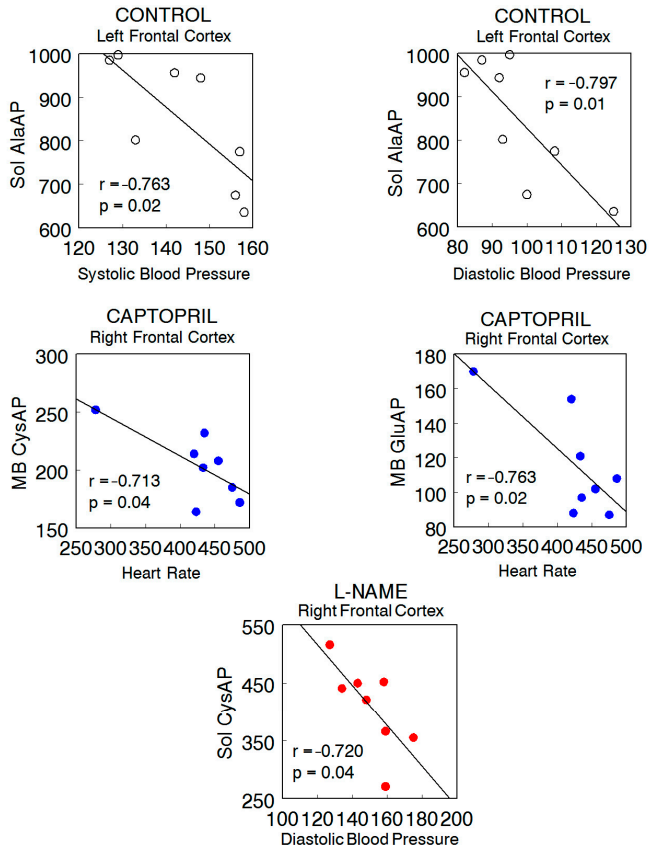

Figure 3. Significant correlations between neuropeptidase activities of the left or right frontal cortex with the different parameters studied in WKY rats. Each of the four treatment groups (n = 8 each) were considered independently. Control (open circles), captopril (blue circles), L-NAME (red circles). The figures indicate the significant correlations between specific soluble (Sol) or membrane-bound (MB) alanyl-(AlaAP), cystinyl-(CysAP), or glutamyl-(GluAP) aminopeptidase activities, expressed as pmol/min/mg prot, of the left or right frontal cortex versus systolic blood pressure, diastolic blood pressure (mmHg) or heart rate (beats/min) values. Pearson's correlation coefficients (r) and p values are indicated into each figure. Propranolol treatment did not show any significant correlation.

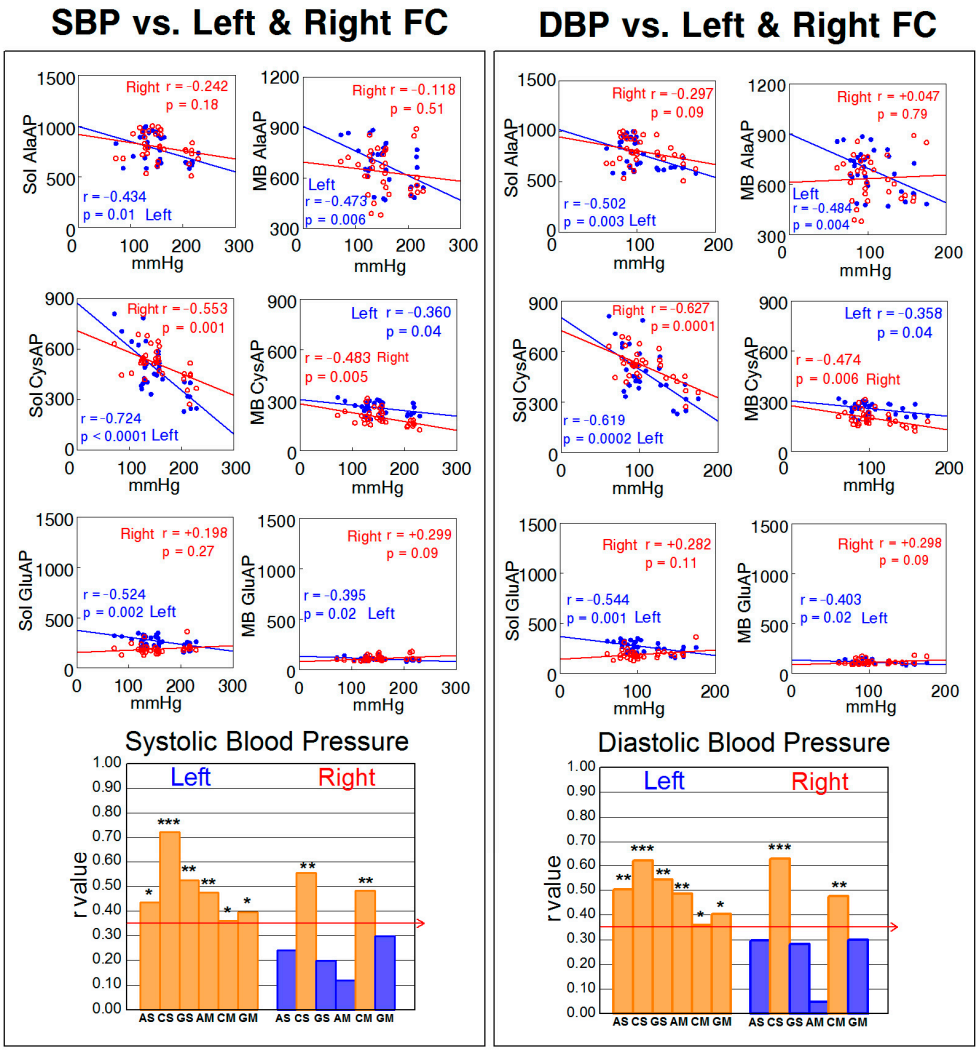

Figure 4. Correlations between angiotensinase activities of the left or right frontal cortices versus systolic or diastolic blood pressure, regardless of drug treatments. Correlations between SBP (left panel) and DBP (right panel) (n = 32) vs. left (n = 32) or right (n = 32) neuropeptidase activities of the frontal cortex (FC) considering together all the data of the four treated and untreated groups studied for each activity. The top figures indicate the correlations between specific soluble (left figures, Sol) or membrane-bound (right figures, MB) alanyl-(AlaAP), cystinyl-(CysAP) or glutamyl-(GluAP) aminopeptidase activities, expressed as pmol/min/mg prot, of the left (blue lines and close circles) and right (red lines and open circles) FC versus SBP or DBP values (mmHg). r and *p* values of the left (blue) and right (red) FC are indicated in each figure. In the bottom figures of the left and right panels, the *y*-axis indicates the r values of the correlations between SBP or DBP versus the enzymatic activities analysed, without considering if it has positive or negative character. In the X axis, the different soluble (S) or membrane-bound (M) activities of the left or right FC are indicated. The red arrow crossing the bars, indicates the level of r above which, the correlation reaches statistical significance (rose bars). Blue bars below arrow indicate no significance. A, alanyl-, C, cystinyl-, G, glutamyl-aminopeptidase. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

4. Discussion

In the present research, LN treatment significantly increased SBP and DBP and decreased HR. However, propranolol did not modify any parameters although the dosage was reported to be efficacious [12]. We cannot clearly explain such behavior but other authors have also described similar results and suggested that propranolol influence on cardiac function may be variable depending on several factors, for example, the place of breeding or the age of the rat [16–18]. Our results show that there are no significant correlations

between the FC and cardiac function after propranolol treatment. However, the results also show that regardless of treatments, the relationship between neuropeptidase activities of the FC and cardiac function is asymmetric and generally negative, which contrasts with the also asymmetric, but positive, relationship established with other physiological processes, such as those related to water balance [4], as discussed below.

We provide evidence for an asymmetrical negative relationship between some brain neuropeptidase activities, reported as regulatory enzymes of neuropeptides involved in cognitive functions and cardio-vascular processes (and vice versa). As a whole, these results would suggest that an increase in systolic and diastolic blood pressure levels would be related to a decrease in some neuropeptidase activities of the frontal cortex, mostly of the left side. This suggests a lower metabolism (longer action) of their endogenous substrates (such as angiotensins, enkephalins, or oxytocin) and, consequently, a longer action of the functions they exert in the left side of the frontal cortex. The results also suggest the contrary: the decrease of SBP and DBP would be related to the increase of neuropeptidase activities (higher activity, higher metabolism/shorter action of the substrate), mostly of the left side.

The blood pressure involves the control of the ventricular contraction strength, heart rate frequency and peripheral resistance. These factors are regulated in part by the autonomic nervous system (ANS). If there is an asymmetrically organized connection between the frontal cortex and SBP or DBP, this may involve the ANS. Indeed, several studies describe such asymmetries in the axis connecting the frontal cortex with the heart through the ANS. It has been reported that the sympathetic activity is essentially controlled by the right hemisphere and the parasympathetic by the left one [19,20]. There is also an asymmetry in the integration of cardiovascular responses to stress showing a predominance of the right dorsomedial hypothalamus [21]. This asymmetrical behavior in cardio-vascular control could also imply partially the brain dopaminergic system. In fact, dopamine depletions of the left hemisphere increased markedly the SBP of rats [22]. Additionally, tyrosine hydroxylase activity was significantly lower in the left mediobasal hypothalamus than in the right one [23]. The specialization of the right frontal cortex in the neuroendocrine and autonomic activation of the stress response involving the mesocortical dopamine system was also reported [5]. These results have been related to the pathogeny of depression in which there are (1) disruptions of the stress regulatory systems involving dopamine, (2) left/right imbalances of the frontal cortex activity and (3) changes in blood pressure levels [8,24]. It is, therefore, accepted that depression involves autonomic disorders leading to cardio-vascular alterations (and vice versa) which may imply a bidirectional frontal cortex-cardio-vascular connection [25] that, according to the present results, would be asymmetrically organized. However, the present data also demonstrate a significant bilateral connection between both the left and right FC CysAP activity and blood pressure. This enzyme activity has been also directly involved in glucose uptake, which may explain in part this special symmetrical bilateral behavior. In fact, the reported results on brain glucose behavior are apparently controversial and some of them could suggest a symmetrical procedure under certain conditions and regions. Ross et al. [26] detected an increase in glucose uptake in the left frontal cortex of female rats, but not in males. In humans, cortical glucose metabolism was essentially symmetric in young children, but turns out to be asymmetric with increasing age. Particularly, the frontal cortex showed an age-related increase of left versus right glucose uptake, while in occipital, parietal, and temporal cortex it was the right which prevailed versus the left side [27].

The present results suggest a general tendency towards the predominance of some left FC neuropeptidase activities for the cardio-vascular control. The brain-heart connection involves a relationship between the cardio-vascular hemodynamic and the cognitive status of the subject. In general terms, while cardio-vascular disruptions are related to a decline in the cognitive processes and development of alterations such as depression or anxiety, the improvement of the cardio-vascular function after treatment of those disruptions increases the cognitive function and alleviates the symptoms [28]. The bilateral interaction between

the left and right FC could be involved in both the development of such disorders and their improvement [8]. Our results demonstrate the existence of such a bidirectional asymmetry in the connection between some neuropeptidases of the frontal cortex and the cardio-vascular function, involving mostly the left frontal cortex. They also show that some enzymatic activities, such as Sol and MB CysAP, and consequently their biological functions, can involve both hemispheres.

The present results also reflect an interesting and remarkable circumstance since they contrast drastically with previously reported results demonstrating significant positive correlations between the left frontal cortex and other peripheral functions such as those related to aqueous balance as water intake and diuresis [4]. In this regard, it should be taken into account that the increased left cortex activity increases parasympathetic activity. As a consequence, it decreases cardio-vascular function. It is clear that stimulation of the parasympathetic decreases heart rate [29] but increases diuresis. Indeed, cervical vagotomy decreases water diuresis [30]. Although correlation does not necessarily imply causation, this may be suggestive of a relationship between variables. Therefore, the present results together with previous ones, may reflect an asymmetrical bidirectional connection between brain and the rest of the organism, presumably mediated by the ANS [4,31,32].

In summary, the neurovisceral integration (NI) model that implies a connection between cardiac function (heart rate variability) and brain function (cognitive performance and emotional health) has been widely studied [1,33]. Anatomical and computational studies support vagal control for such integration [33,34]. Subsequently, a new aspect was provided to understand the mechanism underlying NI, suggesting a neurochemical interaction between neuropeptidase activities of the hypothalamus, heart, and kidney that would also involve the participation of their neuropeptidergic substrates [2]. Such results support the involvement of the ANS in the NI model. As a proposal for the mechanism involved in the functioning of NI, the participation of anterograde and retrograde axonal transport of these enzymes, as well as their substrates, between the brain and peripheral tissues was suggested. This suggestion is supported for example by the fact that a bidirectional axonal transport has been described for angiotensin II [35] and for a proteolytic enzyme [36]. Subsequently, various data suggested that NI, involving the renin-angiotensin system, is carried out asymmetrically [9]. With the present neurochemical/functional data it could be suggested that the heart function might therefore influence asymmetrically the cognitive status, and vice versa. Since angiotensin and its metabolites (as substrates of the measured neuropeptidases) of the frontal cortex may be involved in cognitive functions [37], their asymmetries may also be reciprocally related to the cardio-vascular functions [38]. More recently, data have been provided that correlate asymmetrically the frontal cortex with peripheral metabolic factors, suggesting an asymmetric integrative function of the entire organism [4]. With this research, new and important aspects are provided that help to understand the complex scenery that the concept of NI implies.

5. Conclusions

In our study, the existence of a bidirectional asymmetry in the connection between some brain neuropeptidases and the cardio-vascular function is suggested. Specifically, the SBP and DBP correlate *negatively* and mainly with neuropeptidase activities of the left frontal cortex and, consequently, might be associated with the functions in which these enzymes are involved in that side and vice versa. In addition, these results together with the previous ones showing *positive* correlations between the same neuropeptidase activities of the frontal cortex and water balance functions, strongly support the involvement of the ANS in a bidirectional asymmetric organization of the neurovisceral organization of the organism. Due to the different cognitive and autonomic functions in which the left or right frontal cortices are involved, a deep knowledge of this asymmetric organization could be useful to improve our understanding of certain brain and peripheral disorders (which may be bidirectionally connected) and allow to develop new therapeutic strategies.

Author Contributions: Conceptualization, M.R.-S.; methodology, M.R.-S. and I.P.; software, M.R.-S., I.P., A.B.S., I.B., M.M.-C. and M.d.G.; validation, M.R.-S., I.P., A.B.S., I.B., M.M.-C. and M.d.G.; formal analysis, M.R.-S., I.P., A.B.S., I.B., M.M.-C. and M.d.G.; investigation, M.R.-S., A.B.S. and I.P.; resources, M.R.-S. and I.P.; data curation, M.R.-S. and A.B.S.; writing—original draft preparation, M.R.-S.; writing—review and editing, M.R.-S., I.P., A.B.S., I.B., M.M.-C. and M.d.G.; visualization, M.R.-S.; supervision, M.R.-S., I.P., A.B.S., I.B., M.M.-C. and M.d.G.; project administration, M.R.-S.; funding acquisition, M.R.-S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by the Ministry of Science and Innovation through project no. SAF 2008 04685 C02 01.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the University of Jaén (MEC. Plan Nacional I+D+I 2008-2011; date of approval: 9 January 2008).

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Thayer, J.F.; Lane, R.D. Claude Bernard and the heart-brain connection: Further elaboration of a model of neurovisceral integration. *Neurosci. Biobehav. Rev.* **2009**, *33*, 81–88. [CrossRef]
2. Prieto, I.; Villarejo, A.B.; Segarra, A.B.; Banegas, I.; Wangensteen, R.; Martinez-Cañamero, M.; de Gasparo, M.; Vives, F.; Ramírez-Sánchez, M. Brain, heart and kidney correlate for the control of blood pressure and water balance: Role of angiotensinases. *Neuroendocrinology* **2014**, *100*, 198–208. [CrossRef]
3. Segarra, A.B.; Prieto, I.; Banegas, I.; Villarejo, A.B.; Wangensteen, R.; de Gasparo, M.; Vives, F.; Ramírez-Sánchez, M. The brain-heart connection: Frontal cortex and left ventricle angiotensinase activities in control and captopril-treated hypertensive rats-a bilateral study. *Int. J. Hypertens.* **2013**, *2013*, 156179. [CrossRef] [PubMed]
4. Segarra, A.B.; Prieto-Gomez, I.; Banegas, I.; Martínez-Cañamero, M.; Luna, J.D.; de Gasparo, M.; Ramírez-Sánchez, M. Functional and neurometabolic asymmetry in SHR and WKY rats following vasoactive treatments. *Sci. Rep.* **2019**, *9*, 16098. [CrossRef] [PubMed]
5. Sullivan, R.M. Hemispheric asymmetry in stress processing in rat prefrontal cortex and the role of mesocortical dopamine. *Stress* **2004**, *7*, 131–143. [CrossRef] [PubMed]
6. Denenberg, V.H. Hemispheric laterality in animals and the effects of early experience. *Behav. Brain Sci.* **1981**, *4*, 1–49. [CrossRef]
7. Rogers, L.J.; Vallortigara, G.; Andrew, R.J. Divided Brains. In *The Biology and Behaviour of Brain Asymmetries*; Cambridge University Press: Cambridge, UK, 2013.
8. Prieto, I.; Segarra, A.B.; Villarejo, A.B.; de Gasparo, M.; Martínez-Cañamero, M.M.; Ramírez-Sánchez, M. Neuropeptidase activity in the frontal cortex of Wistar-Kyoto and spontaneously hypertensive rats treated with vasoactive drugs: A bilateral study. *J. Hypertens.* **2019**, *37*, 612–628. [CrossRef] [PubMed]
9. Ramírez-Sánchez, M.; Prieto, I.; Wangensteen, R.; Banegas, I.; Segarra, A.B.; Villarejo, A.B.; Vives, F.; Cobo, J.; de Gasparo, M. The renin-angiotensin system: New insight into old therapies. *Curr. Med. Chem.* **2013**, *20*, 1313–1322. [CrossRef]
10. Chai, S.Y.; Fernando, R.; Peck, G.; Ye, S.Y.; Mendelsohn, F.A.; Jenkins, T.A.; Albiston, A.L. The angiotensin IV/AT4 receptor. *Cell. Mol. Life Sci.* **2004**, *61*, 2728–2737. [CrossRef]
11. Eshima, K.; Hirooka, Y.; Shigematsu, H.; Matsuo, I.; Koike, G.; Sakai, K.; Takeshita, A. Angiotensin in the nucleus tractus solitarii contributes to neurogenic hypertension caused by chronic nitric oxide synthase inhibition. *Hypertension* **2000**, *36*, 259–263. [CrossRef]
12. Priviero, F.B.; Teixeira, C.E.; Claudino, M.A.; De Nucci, G.; Zanesco, A.; Antunes, E. Vascular effects of long-term propranolol administration after chronic nitric oxide blockade. *Eur. J. Pharmacol.* **2007**, *571*, 189–196. [CrossRef] [PubMed]
13. Domínguez-Vías, G.; Aretxaga-Maza, G.; Prieto, I.; Luna, J.D.; de Gasparo, M.; Ramírez-Sánchez, M. Diurnal opposite variation between angiotensinase activities in photo-neuro-endocrine tissues of rats. *Chronobiol. Int.* **2017**, *34*, 1180–1186. [CrossRef] [PubMed]
14. Ramírez, M.; Prieto, I.; Banegas, I.; Segarra, A.B.; Alba, F. Neuropeptidases. *Methods Mol. Biol.* **2011**, *789*, 287–294. [PubMed]
15. Paxinos, G.; Watson, C. *The Rat Brain in Stereotaxic Coordinates*, 4th ed.; Academic Press: London, UK, 1998.
16. Weiss, L.; Lundgren, Y.; Folkow, B. Effects of prolonged treatment with adrenergic beta-receptor antagonists on blood pressure, cardiovascular design and reactivity in spontaneously hypertensive rats (SHR). *Acta Physiol. Scand.* **1974**, *91*, 447–457. [CrossRef] [PubMed]

17. DeBlois, D.; Tea, B.S.; Than, V.D.; Tremblay, J.; Hamet, P. Smooth muscle apoptosis during vascular regression in spontaneously hypertensive rats. *Hypertension* **1997**, *29*, 340–349. [CrossRef]
18. Slaiby, J.M.; Ricci, M.A.; Gadowski, G.R.; Hendley, E.D.; Pilcher, D.B. Expansion of aortic aneurysms is reduced by propranolol in a hypertensive rat model. *J. Vasc. Surg.* **1994**, *20*, 178–183. [CrossRef]
19. Wittling, W.; Block, A.; Genzel, S.; Schweiger, E. Hemisphere asymmetry in parasympathetic control of the heart. *Neuropsychologia* **1998**, *36*, 461–468. [CrossRef]
20. Diedrich, A.; Porta, A.; Barbic, F.; Brychta, R.J.; Bonizzi, P.; Diedrich, L.; Cerutti, S.; Robertson, D.; Furlan, R. Lateralization of expression of neural sympathetic activity to the vessels and effects of carotid baroreceptor stimulation. *Am. J. Physiol. Heart Circ. Physiol.* **2009**, *296*, H1758–H1765. [CrossRef] [PubMed]
21. Xavier, C.H.; Beig, M.I.; Ianzer, D.; Fontes, M.A.; Nalivaiko, E. Asymmetry in the control of cardiac performance by dorsomedial hypothalamus. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2013**, *304*, R664–R674. [CrossRef] [PubMed]
22. Banegas, I.; Prieto, I.; Segarra, A.B.; Durán, R.; Vives, F.; Alba, F.; Luna, J.D.; de Gasparo, M.; Wangensteen, R.; Ruiz-Bailen, M.; et al. Blood pressure increased dramatically in hypertensive rats after left hemisphere lesions with 6-hydroxydopamine. *Neurosci. Lett.* **2011**, *500*, 148–150. [CrossRef] [PubMed]
23. Alexander, N.; Kaneda, N.; Ishii, A.; Mogi, M.; Harada, M.; Nagatsu, T. Right-left asymmetry of tyrosine hydroxylase in rat median eminence: Influence of arterial baroreflex nerves. *Brain Res.* **1990**, *523*, 195–198. [CrossRef]
24. Sullivan, R.M.; Gratton, A. Lateralized effects of medial prefrontal cortex lesions on neuroendocrine and autonomic stress responses in rats. *J. Neurosci.* **1999**, *19*, 2834–2840. [CrossRef] [PubMed]
25. Iseger, T.A.; van Bueren, N.E.R.; Kenemans, J.L.; Gevirtz, R.; Arns, M. A frontal-vagal network theory for major depressive disorder: Implications for optimizing neuromodulation techniques. *Brain Stimul.* **2020**, *13*, 1–9. [CrossRef] [PubMed]
26. Ross, D.A.; Glick, S.D.; Meibach, R.C. Sexually dimorphic brain and behavioural asymmetries in the neonatal rat. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 1958–1961. [CrossRef]
27. Pilli, V.K.; Jeong, J.W.; Konka, P.; Kumar, A.; Chugani, H.T.; Juhász, C. Objective PET study of glucose metabolism asymmetries in children with epilepsy: Implications for normal brain development. *Hum. Brain Mapp.* **2019**, *40*, 53–64. [CrossRef]
28. Hooghiemstra, A.M.; Bertens, A.S.; Leeuwis, A.E.; Bron, E.E.; Bots, M.L.; Brunner-La Rocca, H.P.; de Craen, A.J.M.; van der Geest, R.J.; Greving, J.P.; Kappelle, L.J.; et al. Heart-brain connection consortium, the missing link in the pathophysiology of vascular cognitive impairment: Design of the heart-brain study. *Cerebrovasc. Dis. Extra* **2017**, *7*, 140–152. [CrossRef]
29. Gordan, R.; Gwathmey, J.K.; Xie, L.H. Autonomic and endocrine control of cardiovascular function. *World J. Cardiol.* **2015**, *7*, 204–214. [CrossRef]
30. Schrier, R.W.; Berl, T. Mechanism of the antidiuretic effect associated with interruption of parasympathetic pathways. *J. Clin. Investig.* **1972**, *51*, 2613–2620. [CrossRef]
31. Prieto, I.; Segarra, A.B.; Martinez-Canamero, M.; de Gasparo, M.; Zorad, S.; Ramirez-Sanchez, M. Bidirectional asymmetry in the neurovisceral communication for the cardiovascular control: New insights. *Endocr. Regul.* **2017**, *51*, 157–167. [CrossRef]
32. Banegas, I.; Prieto, I.; Segarra, A.B.; Martínez-Cañamero, M.; de Gasparo, M.; Ramírez-Sánchez, M. Angiotensin II, dopamine and nitric oxide. An asymmetrical neurovisceral interaction between brain and plasma to regulate blood pressure. *Aims Neurosci.* **2019**, *6*, 116–127. [CrossRef]
33. Smith, R.; Thayer, J.F.; Khalsa, S.S.; Lane, R.D. The hierarchical basis of neurovisceral integration. *Neurosci. Biobehav. Rev.* **2017**, *75*, 274–296. [CrossRef] [PubMed]
34. Richter, F.; García, A.M.; Rodriguez Arriagada, N.; Yoris, A.; Birba, A.; Huepe, D.; Zimmer, H.; Ibáñez, A.; Sedeño, L. Behavioral and neurophysiological signatures of interoceptive enhancements following vagus nerve stimulation. In *Human Brain Mapping*; Wiley Periodicals LLC: New York, NY, USA, 2020; Epub ahead of print.
35. Diz, D.I.; Ferrario, C.M. Bidirectional transport of angiotensin II binding sites in the vagus nerve. *Hypertension* **1988**, *11*, I139–I143. [CrossRef] [PubMed]
36. Hung, C.O.; Coleman, M.P. KIF1A mediates axonal transport of BACE1 and identification of independently moving cargoes in living SCG neurons. *Traffic* **2016**, *17*, 1155–1167. [CrossRef] [PubMed]
37. Sudilovsky, A.; Turnbull, B.; Croog, S.H.; Crook, T. Angiotensin converting enzyme and memory: Preclinical and clinical data. *Int. J. Neurol.* **1987**, *21–22*, 145–162.
38. Craig, A.D. Forebrain emotional asymmetry: A neuroanatomical basis? *Trends Cogn. Sci.* **2005**, *9*, 566–571. [CrossRef]