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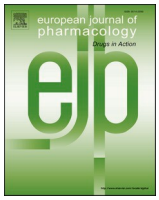

Sodium valproate reverses aortic hypercontractility in acute myocardial infarction in rabbits

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ABSTRACT

Sympathetic nervous system (SNS), endothelin 1 (ET-1) and angiotensin II (Ang II) are involved in the pathophysiology of acute myocardial infarction (AMI). Valproic acid (VPA) is under study for the treatment against AMI due to its beneficial cardiac effects. However, the vascular effects of VPA on the activation of the SNS, ET-1 and Ang II after AMI are not fully studied. In our study, we used aorta from New Zealand White rabbits without AMI, with AMI and AMI treated with VPA (500 mg/kg/day). AMI was induced by occluding the left circumflex coronary artery for 1 h, followed by reperfusion. After 5 weeks, we studied the ex vivo vascular reactivity in organ bath and measured protein expression by Western blot. Our findings indicated that AMI increased vasoconstriction to exogenous and endogenous NE and ET-1, which was reversed by VPA eliciting upregulation of α_2-adrenergic and ETB receptors and downregulating ETA receptors. Although no changes in the vascular response to Ang II were observed in AMI or VPA-treated rabbits, an increase in Ang II type 2 receptor expression was found in VPA-treated rabbits. We conclude that VPA could be considered a vascular protector by modulating SNS, ET-1 and Ang II in the aorta, which together with its cardioprotective effect would make it a promising candidate for the treatment of AMI.

1. Introduction

The number of patients with heart failure continues to increase due to the growth and ageing of the population, being acute myocardial infarction (AMI) the main contributor to heart failure (Groenewegen et al., 2020; Yin et al., 2023). Sympathetic nervous system (SNS), endothelin 1 (ET-1) and angiotensin II (Ang II) are involved in the pathophysiology of AMI. The reduction in the cardiac output after AMI activates the SNS, resulting in compensatory increased heart rate, myocardial contractility and oxygen consumption. However, sustained sympathetic activation stimulates myocardial interstitial fibrosis leading to the development of heart failure (Jiang et al., 2023).

Myocardial ischaemia causes norepinephrine (NE) release from sympathetic nerve endings and ET-1 plays an important role in this process, by increasing NE release via activation of endothelin A (ETA) receptor and decreasing NE overflow via endothelin B (ETB) receptor (Tawa et al., 2012). In addition, ET-1 has direct effect in ventricular cardiomyocytes (Proven et al., 2006) and it is a potent vasoconstrictor, leading to coronary vasoconstriction that underlies myocardial ischaemia and ventricular dysfunction (Doggrell, 2004). In fact, both ET-1 levels and ETA receptor expression are increased in AMI (Leary et al., 2020). Moreover, as occurs with NE and ET-1, Ang II levels are also elevated in AMI (Deng et al., 2022). Ang II induces an increase in ventricular wall stress by acting through a receptor-mediated signal transduction system and results in the development of cardiac hypertrophy (Shah et al., 2021). Ang II, mediates its functions by binding to its G protein-coupled receptors (Pugliese et al., 2020). Activation of the Ang II type 1 receptor (ATR1) increases the proinflammatory response

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and aldosterone levels, while activation of the type 2 receptor (ATR2) has anti-fibrotic and anti-inflammatory effects (Ziaja et al., 2021).

Valproic acid or sodium valproate (VPA) is a branched-chain carboxylic acid, used as an anti-epileptic drug, which has been shown to inhibit histone deacetylase (HDAC). A growing number of recent studies have shown that HDAC inhibitors improve heart diseases including AMI (see the review (Chun, 2020)). We have previously shown that VPA treatment enhances nitric oxide (NO) bioavailability and reverses the AMI-induced endothelial dysfunction (Guerra-Ojeda et al., 2024). However, the vascular effect of VPA on the activation of the SNS, ET-1 and Ang II systems after AMI is unknown. In the current paper, we hypothesise that VPA could modify the response to these systems leading to a protective effect against excessive constriction.

2. Material and methods

2.1. Animal procedures

All procedures were approved by the Institutional Animal Care and Use Committee of the University of Valencia (2015/VSC/PEA/00233 type 2) in compliance with the European Union directive 2010/63 on the protection of animals used for scientific purposes. 15-week-old male New Zealand white rabbits (n = 30) weighing 3–3.5 kg, were randomly distributed into three experimental groups: the SHAM operated group (n = 10), the AMI group (n = 10) and the AMI + VPA group (n = 10). All rabbits were housed under controlled and constant conditions of temperature (room temperature 19 ± 2 °C), relative humidity (55 ± 10%) and artificial light-dark cycles of 12h. Standard chow and water were available *ad libitum*. The surgical procedure was performed under the same experimental conditions in all three groups. While in the AMI and AMI + VPA groups, myocardial infarction was induced by ligation of the left circumflex coronary artery, in the SHAM group, rabbits underwent the same surgical procedure but without arterial ligation as previously described (Genovés et al., 2020). Rabbits in the AMI + VPA group were treated with VPA (500 mg/kg/24h) for 5 weeks until sacrifice (further details can be found in the Supplementary Material). The surgical procedure used in this study has proven effective in inducing some of the haemodynamic and biochemical manifestations of AMI as well as histopathological changes in cardiac tissue (Genovés et al., 2020).

2.2. Collection of samples

After 5 weeks of the surgical procedure the rabbits were euthanized with sodium thiopental (60 mg/kg IV) and, after laparotomy, the abdominal aorta was dissected and placed in chilled saline (4 °C). The aorta was then carefully isolated from the perivascular adipose tissue. An aortic segment of ~5 mm was frozen in liquid nitrogen and stored at −80 °C until protein expression analysis. The remaining aortic tissue was cut into ~3 mm rings used for isometric tension recording in organ baths.

2.3. Organ bath study

Aortic rings were mounted in organ baths with two L-shaped stainless-steel wires as previously described (Marchio et al., 2018), in Krebs-Henseleit solution containing (in mM): NaCl, 115; KCl, 4.6; $MgCl_2 \bullet 6H_2O$, 1.2; $CaCl_2$, 2.5; $NaHCO_3$, 25; glucose 11.1 and disodium EDTA, 0.01(pH 7.30–7.40 at 37 °C). The solution was gassed with 95% O_2 and 5% CO_2 at 37 °C. The arteries were allowed to equilibrate for 1 h to a resting tension of 3 g and changes in isometric force generation were recorded at 10 Hz using a PowerLab/8e data acquisition system (ADInstruments, New Zealand) and LabChart software (v7.2.5, ADInstruments, New Zealand). The vessel contractility was evaluated by the response to potassium chloride (KCl, 60 mM). Endothelial health was assessed using acetylcholine (ACh, 10^{-6} M) following preconstriction to NE (10^{-7} to $3X10^{-7}$ M) to reach ~75% of the maximal contraction to KCl. Only arteries which exhibited robust and maintained contraction to KCl and relaxation to ACh >70% were considered viable for further experimentation. Vascular reactivity was assessed by cumulative response to NE (10^{-9} to 10^{-4} M), ET-1 (10^{-11} to 10^{-7} M) and Ang II (10^{-11} to 10^{-6} M). Responses to agonists were obtained from different rings.

2.4. Measurement of neurogenic tone by electrical field stimulation

For electrical field stimulation (EFS) of sympathetic nerves to induce neurogenic tone, arteries were prepared as previously described (Mauricio et al., 2007). EFS was applied by a Grass S88 stimulator (Grass Instruments) via two platinum electrodes positioned on each side and parallel to the axis of the arterial ring. Single square wave pulses (0.25 ms pulse duration, 4–8Hz, at a supramaximal voltage of 20 V) were used. The train duration was 30 s with a stimulation interval of 5 min. In these conditions, EFS was applied to the aortic rings from all groups. To test whether the EFS-induced vasoconstriction is of sympathetic nervous origin, a previous set of EFS experiments was incubated with tetrodotoxin (10-6 M), a Na + voltage-dependent channel blocker, guanethidine (10-6 M) to block transmission in postganglionic adrenergic nerves and prazosin (10-6 M) a selective α1-adrenergic receptor (AR) antagonist. The reduced EFS-induced vasoconstriction indicated a neurogenic contractile response triggering NE release from perivascular nerves that activates the α1-AR, and not a direct stimulus on vascular smooth muscle.

2.5. Western blot analysis

Aortic tissue samples from the three groups were homogenized in lysis buffer (0.125 M Tris-HCl, pH 6.8, 2% SDS, 19% glycerol and 1% v/v protease inhibitors). Tissue lysates were centrifuged at 12,000 rpm for 20 min at 4 °C. Protein concentrations were determined using bicinchoninic acid protein assay (ThermoFisher, USA). Proteins (40 μg) were separated on SDS-PAGE gels and transferred to polyvinylidene fluoride membranes. Subsequently, the membranes were blocked for 1 h at room temperature with blocking buffer (5% non-fat dry milk, 0.1% Tween-20 in Tris-buffered solution), followed by incubation overnight at 4 °C with primary antibody against either α_{1A}-adrenergic (1:1000, Cat #NB100-78585, NovusBio), α_{2A}-adrenergic (1:1000, Cat #NBP2-22452, NovusBio), ETA receptor (1:1000, Cat #Ab85163, Abcam), ETB receptor (1:5000, Cat #Ab117529, Abcam), ATR1 (1:1000, #PA5-20812, ThermoFisher), ATR2 (1:2000, #PA5-20813, ThermoFisher) and β-actin (1:5000, Cat #NB-600-501SS, NovusBio). After incubation with corresponding secondary antibodies for 1 h at room temperature, bands were detected by chemiluminescence method (Amersham Biosciences) and visualized by the digital image system ImageQuant LAS 4000 (GE Healthcare). Protein expression was quantified by densitometry using ImageJ (National Institutes of Health, Bethesda, MD, USA). β-actin was used as a protein loading control.

2.6. Drugs and solutions

All drugs were obtained from Sigma-Aldrich except for potassium chloride, which was purchased from Panreac, and were dissolved in distilled water. Stock solutions were prepared daily in saline solution prior to use and kept on ice throughout the experiment. Inhibitors were incubated with the tissue for at least 30 min.

2.7. Statistical analysis

Data were analysed using GraphPad Prism (v 8.0.2, GraphPad Software, USA). Results are presented as mean ± standard error of mean (SEM) for vascular reactivity experiments and mean ± standard deviation (SD) for protein expression analysis. Contractions were expressed as a percentage relative to the value of the maximum effect to KCl (60 mM).

Sample size (n) is indicative of the number of animals. Statistical comparisons were made using one-way or two-way analysis of variance (ANOVA) as appropriate, with Bonferroni post-test for multiple comparisons. $P < 0.05$ was considered statistically significant.

3. Results

3.1. VPA treatment reverses the increased adrenergic response induced by AMI

To investigate the effect of VPA on NE-mediated vasoconstriction, aortic rings from all groups were assayed for responsiveness to cumulative response to NE (10^{-9} to 10^{-4} M). Vasoconstriction in response to NE was significantly increased in aortas from *AMI* group compared to SHAM (maximum effect from 183.75 ± 8.49% to 226.25 ± 9.82%, for SHAM vs AMI $P = 0.0069$). This difference was reversed by VPA treatment (maximum effect from 226.25 ± 9.82% to 171.00 ± 9.87%, for AMI vs AMI + VPA $P = 0.0069$) (Fig. 1A), but with no changes in AMI-induced overexpression of α_1-AR (Fig. 1B).

To investigate whether VPA modulate vasoconstriction to NE release from sympathetic nerve terminals, EFS (4 and 8 Hz) was used on aortic rings from all three groups. EFS-induced contraction was significantly increased in the AMI group which was reversed by VPA treatment (SHAM, 8.75 ± 1.10 % vs AMI, 13.67 ± 1.45 % vs AMI + VPA, 9.12 ± 0.61 %; $P < 0.05$) (Fig. 2A). This response was consistent with an upregulation of α_2-AR expression in aorta from AMI + VPA group (Fig. 2B). Taken together these findings suggest an AMI-induced increase in vascular tone via α_1-AR activation, which is reversed by the VPA-induced increase in α_2-AR.

3.2. VPA diminishes ET-1 potentiated contraction induced by AMI

Cumulative concentration-response curves to ET-1 were performed in aortic rings from all groups to study the effect of VPA after AMI. As expected, the maximal contractile response to ET-1 was significantly increased in the AMI group (maximum effect from 147.66 ± 13.05% to 120.67 ± 3.70%, AMI vs SHAM $P = 0.0373$). However, VPA treatment completely prevented this response by diminishing maximum effect (from 147.66 ± 13.05% to 108.50 ± 4.62%, AMI vs AMI + VPA $P = 0.0002$) (Fig. 3A). These data were consistent with a reduced expression of ETA receptors and increased expression of ETB receptors in the AMI + VPA group compared to the AMI group (Fig. 3B and C).

3.3. Treatment with VPA elicits an overexpression of ATR2

The effect of VPA treatment on the contractile response to Ang II (10^{-10} to 10^{-6} M) was also evaluated. In this case, response to Ang II was not modified in any of the groups, although a tendency to decrease was observed in the AMI group (Fig. 4A). However, aortic tissue from the AMI group showed no evidence of reduced ATR1 expression (Fig. 4B), whereas a significant increase in ATR2 expression was found in the AMI + VPA group (Fig. 4C).

4. Discussion

Overall, our findings indicate that AMI induces a higher vasoconstriction in response to NE and ET-1 in aorta from rabbits, and that VPA treatment reverses these effects. Since NE (Ostrowski et al., 2013) and ET-1 levels (Doggrell, 2004) are increased in AMI patients, VPA could be a protective agent against excessive vasoconstriction mediated by these agonists. Moreover, our results show no changes in vascular response to Ang II in AMI or with VPA treatment. However, ATR2 was upregulated in the presence of VPA. The activation of ATR2 is related to anti-fibrotic and anti-inflammatory effects (Ziaja et al., 2021), and an increase in vasodilation due to a higher release of NO (Carey, 2017). This effect would also play in favour of the vascular protective effect of VPA.

The increased vasocontraction to NE observed in aortic rings from AMI is consistent with a greater protein expression of α_1-AR. However, although VPA treatment did not modify this α_1-AR overexpression, it was able to reduce hypercontractility to NE. Because NE is a non-selective agonist of AR (Guimarães and Moura, 2001) it is reasonable to suggest that it may be activating the α_2-AR. In this regard, we demonstrated that VPA increased α_2-AR expression. Therefore, our results support the idea that the adrenergic action of VPA is mediated by the stimulation of α_2-AR in the endothelium, which induces NO release (Sorriento et al., 2011). The expression of these receptors in the endothelium is variable and increases in vessels exposed to high partial pressures of oxygen and high blood flow, such as in the aorta (Vanhoutte and Miller, 1989). Consequently, the VPA action on α_2-AR would counteract the AMI-induced hypercontractility in response to NE.

In addition to the vasculature, α_2-AR are also localized at the prejunctional level acting as autoreceptors that, when activated by NE, inhibit subsequent release of NE induced by a sympathetic nerve impulse (Gilsbach and Hein, 2008). In this sense, we observed that VPA treatment was able to reverse the increased contraction induced by EFS

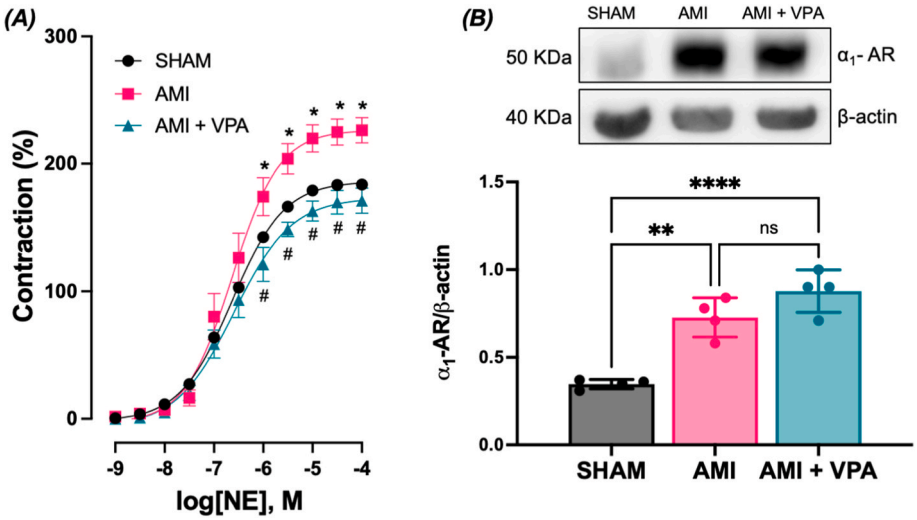

Fig. 1. (A) Contraction-response curves to cumulative NE (10^{-9} to 10^{-4} M) in aortic rings from all groups. Data are means ± SEM (n = 8 arteries from different rabbits); *P < 0.05 vs SHAM and #P < 0.05 vs AMI. (B) Representative Western blot for α_1-AR proteins in aortic tissue from all groups; β-actin was used as internal control. Data are means ± SD (n = 4 arteries from different rabbits); **P < 0.01 and ***P < 0.001 vs SHAM.

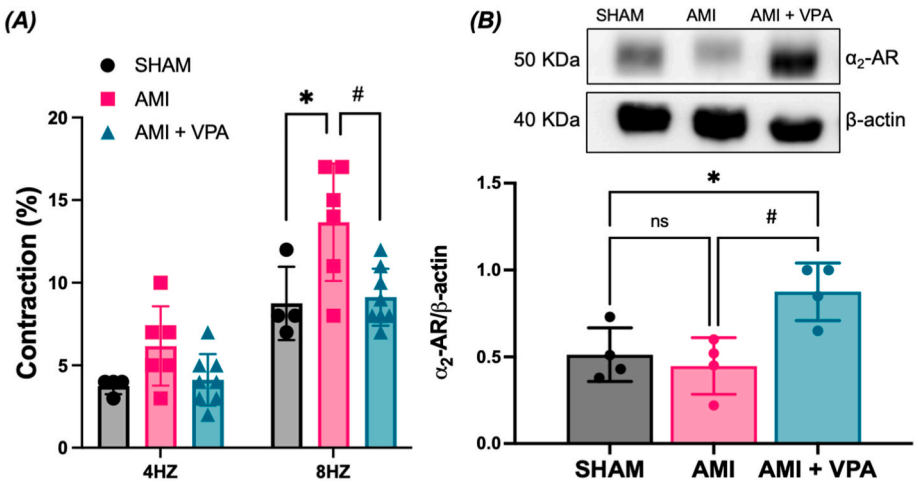

Fig. 2. (A) Bar graph summarizing EFS-induced contraction in aortic rings from all groups. Data are means ± SEM (n = 4 to 8 arteries from different rabbits); *P < 0.05 vs SHAM and #P < 0.05 vs AMI. (B) Representative Western blot for α_2-AR proteins in aortic tissue from all groups; β-actin was used as internal control. Data are means ± SD (n = 4 arteries from different rabbits); *P < 0.5 vs SHAM and #P < 0.05 vs AMI.

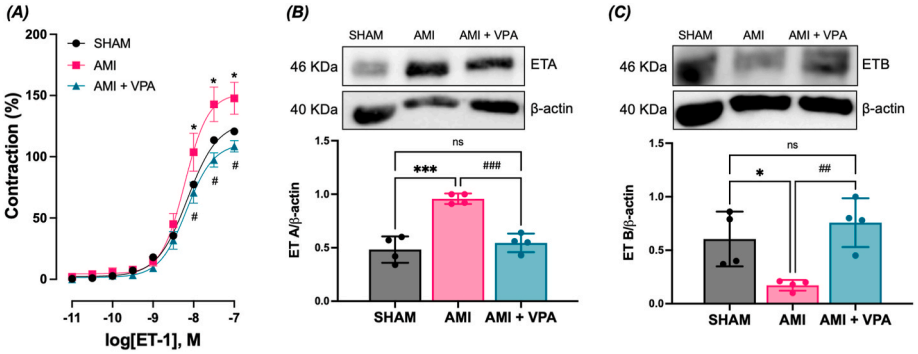

Fig. 3. (A) Contraction-response curves to cumulative ET-1 (10^{-11} to 10^{-7} M) in aortic rings from all groups. Data are means ± SEM (n = 4 to 6 arteries from different rabbits); *P < 0.05 vs SHAM and #P < 0.05 vs AMI. Representative Western blot for (B) ETA and (C) ETB proteins in aortic tissue from all groups; β-actin was used as internal control. Data are means ± SD (n = 4 arteries from different rabbits); *P < 0.005, ***P < 0.001 vs SHAM and ##P < 0.01, ###P < 0.001 vs AMI.

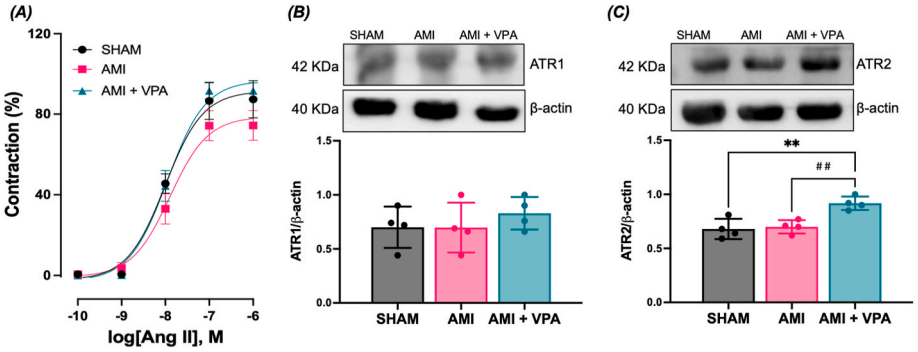

Fig. 4. (A) Contraction-response curves to cumulative Ang II (10^{-10} to 10^{-6} M) in aortic rings from all groups. Data are means ± SEM (n = 5 to 7 arteries from different rabbits). Representative Western blot for (B) ATR1 and (C) ATR2 proteins in aortic tissue from all groups; β-actin was used as internal control. Data are means ± SD (n = 4 arteries from different rabbits); **P < 0.01 vs SHAM and, ##P < 0.01 vs AMI.

in aortic rings from AMI, probably via pre-junctional α_2-AR activation. In this regard, studies that focus on the modulation of the SNS by VPA at the vascular level are scarce. For instance, only one study has speculated that because VPA reduces neuronal injury and has anti-inflammatory and antiapoptotic effects as a histone deacetylase inhibitor, it may have a role in alleviating cardiac remodelling by inhibiting sympathetic activity (Liu et al., 2017). Furthermore, although it has been shown that VPA can attenuate hypertension, oxidative stress, and enhance vascular relaxation in rat aorta with transverse aortic constriction (Jung et al., 2019), none of these studies delves into the interaction between VPA and vascular adrenergic receptors. Therefore, our study is probably the first to establish that VPA can increase α_2-AR expression in the aorta after AMI.

According to our results, aorta from AMI group showed a higher contractile response to ET-1, an effect which was reversed by VPA. The analysis of protein expression of the ET-1 receptors indicated an increase

in the ETA receptor in AMI, which was reversed by VPA treatment. This could explain the hypercontractility in response to ET-1 in AMI and the mechanism by which VPA reverses this effect. Moreover, ETB receptor expression decreased in AMI and VPA restored protein levels to SHAM values. This mechanism could also reinforce the vascular improvement attributed to VPA, since the ETB receptor has been related to cardiovascular protective role (Kolettis, 2014). Furthermore, it has been observed that brain ETA receptors modulate sympathetic and vagal responses altering arrhythmogenesis during myocardial necrosis in rats (Lekkas et al., 2019), whereas ETB receptor decreased sympathetic activation and arrhythmogenesis during the early phase of myocardial infarction (Oikonomidis et al., 2010) via NO production (Tawa et al., 2011). Therefore, increased expression of ETA receptors would worsen the prognosis of AMI, whereas increased expression of ETB receptor would improve it. In this regard, our results indicate that VPA may have a beneficial role in the treatment of AMI by modulating ET-1 receptors expression in a cardioprotective manner. However, our experiments were performed at the vascular level and the protective effects of ETB described above are found at the cardiac level. Regarding vessels, it is well known that ET-1 is one of the most potent vasoconstrictors and exerts its biological action through activation of ETA receptors which leads to vasoconstriction and exerts prooxidative actions, while endothelial ETB receptor causes vasodilation due to stimulation of NO and prostacyclin production (Pollock, 2005). This is the first study demonstrating that VPA modulates endothelin system at the vascular level.

Finally, several authors have highlighted the involvement of Ang II in pathophysiological processes of AMI (Forrester et al., 2018; Fontes et al., 2020). Renin-angiotensin-aldosterone system is involved in the genesis and progression of several cardiovascular diseases. When Ang II becomes elevated, eNOS activity decreases and ET-1 levels increases (Maneesai et al., 2016) aggravating the endothelial dysfunction that underlying AMI (Zhou et al., 2014). Surprisingly, we did not find differences in the contractile response to Ang II or protein expression of ATR1 among groups. However, we did observe an increase in ATR2 expression in rabbits with AMI treated with VPA. Since activation of ATR2 has been related to the release of NO (Carey, 2017), VPA may be exerting an important regulatory effect on vasomotor tone by countering, through NO release, the hypercontractility induced by AMI thorough activation of NE and ET-1 systems. In other cardiovascular disorders, such as hypertension induced by high fat diet, the mRNA expression of ATR1 increases and VPA reverses it to normal levels (Choi et al., 2017). However, the modulation of the ATR2 by VPA at the vascular level, as shown in this study, has not been previously described.

5. Conclusions

VPA may act as a vascular protector after AMI by increasing protein expression of α2-AR, ETB and ATR2 receptors, and decreasing ETA receptors. Given that the SNS, ET-1 and Ang II systems are activated after AMI, our study supports the idea that the use of VPA could counteract the excessive vasoconstriction resulting from the activation of these systems.

The results of this paper, together with our previous work (Guerra-Ojeda et al., 2024) showing that VPA improved endothelial function through an antioxidant effect, make VPA a promising drug for the treatment of AMI.

CRediT authorship contribution statement

S. Guerra-Ojeda: Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **A. Suarez:** Methodology, Investigation, Formal analysis, Data curation. **B. Belmonte:** Methodology, Investigation, Formal analysis. **P. Marchio:** Methodology, Investigation, Formal analysis. **P. Genovés:** Methodology, Investigation. **O.J. Arias-Mutis:** Methodology, Investigation. **M. Aldasoro:** Investigation, Funding acquisition. **J.M. Vila:** Writing – review & editing, Supervision, Conceptualization. **E. Serna:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **M.D. Mauricio:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejphar.2024.177216.

Data availability

Data will be made available on request.

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