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The influence of post-infarct heart failure and high fat diet on the expression of apelin APJ and vasopressin V1a and V1b receptors

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ABSTRACT

Vasopressin and apelin are reciprocally regulated hormones which are implicated in the pathophysiology of heart failure and the regulation of metabolism; however, little is known about their interactions under pathological conditions. In this study, we determined how post-infarct heart failure (HF) and a high fat diet (HFD) affect expression of the apelin APJ receptor (APJR) and the V1a (V1aR) and V1b (V1bR) vasopressin receptors in the hypothalamus, the heart, and the retroperitoneal adipose tissue. We performed experiments in male 4-week-old Sprague Dawley rats. The animals received either a normal fat diet (NFD) or a HFD for 8 weeks, then they underwent left coronary artery ligation to induce HF or sham surgery (SO), followed by 4 weeks of NFD or HFD. The HF rats showed higher plasma concentration of NT-proBNP and copeptin. The HF reduced the APJR mRNA expression in the hypothalamus. The APJR and V1aR protein levels in the hypothalamus were regulated both by HF and HFD, while the V1bR protein level in the hypothalamus was mainly influenced by HF. APJR mRNA expression in the heart was significantly higher in rats on HFD, and HFD affected the reduction of the APJR protein level in the right ventricle. The regulation of APJR, V1aR and V1bR expression in the heart and the retroperitoneal adipose tissue were affected by both HF and HFD. Our study demonstrates that HF and HFD cause significant changes in the expression of APJR, V1aR and V1bR, which may have an important influence on the cardiovascular system and metabolism.

1. Introduction

Heart failure is still an important clinical problem. It is estimated that heart failure develops in about 1%–2% of people under 70 years old in highly developed countries. However, in people over 70 years old, the incidence of heart failure is estimated to be as much as 10% (Ponikowski et al., 2016). The main factor for the development of heart failure is myocardial infarction (Ponikowski et al., 2016). A key role in the pathogenesis of many cardiovascular diseases is played by obesity (Morris et al., 2015). A characteristic feature of obesity is the excessive accumulation of adipose tissue in the body (Frühbeck et al., 2013). Recently, adipose tissue has been also recognized as a neuroendocrine organ synthesizing and releasing into circulation many biologically active substances called adipokines, among which apelin seems to be particularly involved in regulation of cardiovascular system and metabolism (Molica et al., 2015).

Apelin and its receptor APJ (APJR) play an important role in the pathogenesis of many cardiovascular diseases, including heart failure (Kuba et al., 2019), although both central and peripheral mechanisms have not yet been fully elucidated. The direct role of apelin/APJR in the pathogenesis of heart failure appears to be confirmed by experimental and clinical studies (Sheikh et al., 2008; Folino et al., 2015). In

Abbreviations: ACTH, adrenocorticotropic hormone; ANP, atrial natriuretic peptide; APJR, apelin receptor; AVP, vasopressin; CNS, central nervous system; DIO, diet-induced obese rats; ELISA, enzyme-linked immunoassay; HIF-1α, hypoxia-inducible factor 1-alpha; HF, post-infarct heart failure; HFD, high fat diet; HF NFD, post-infarct heart failure rats on a normal fat diet; HF HFD, post-infarct heart failure rats on a high fat diet; IL-6, interleukin 6; LV, left ventricle; MAPK, mitogen-activated protein kinases; NT-proBNP, N-terminal pro-brain natriuretic peptide; PI3, inositol triphosphate; PKC, protein kinase C; PVN, paraventricular nucleus; RV, right ventricle; SE, standard error; SO, sham surgeries; SO HFD, sham-operated rats on a high fat diet; SON, supraoptic nucleus; SO NFD, sham-operated rats on a normal fat diet; SP1, specificity protein 1; V1aR, V1a vasopressin receptor; V1bR, V1b vasopressin receptor; V2R, V2 vasopressin receptor

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addition, apelin is increasingly seen as a potential therapeutic agent in patients with heart failure (Seifirad and Masoudkabir, 2013; Ureche et al., 2019). Additionally, it was shown that apelin/APJR can play an important role in the central regulation of metabolism (Valle et al., 2008; Clarke et al., 2009; Reaux-Le Goazigo et al., 2011). Besides its central actions, apelin has been shown to exert systemic effects on glucose and lipid metabolism as well as regulation of insulin secretion *via* its APJR (Bertrand et al., 2015). It appears that a high fat diet can also change the activity and expression of apelin and APJR (Valle et al., 2008; Cudnoch-Jedrzejewska et al., 2015). The protein and mRNA of preproapelin have been detected in the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus, which are also the main place for the synthesis of vasopressin (AVP) (De Mota et al., 2004; Yang et al., 2007). Furthermore, apelin is involved in the downregulation of the activity of vasopressinergic neurons (De Mota et al., 2004).

Vasopressin exerts its effects on the body *via* the V1 (V1a vasopressin receptor, V1aR and V1b vasopressin receptor, V1bR), and V2 receptor. V2 receptors (V2Rs) have been detected mainly in the kidneys. In contrast, the V1aRs are located in many structures of the central nervous system (CNS) as well as in peripheral organs such as the heart, vessels and adipose tissues (Szczepanska-Sadowska et al., 2018; Tran et al., 2016). V1bRs have been found mainly in the pituitary gland where it takes part in the stress response by regulating adrenocorticotropic hormone (ACTH) secretion (Szczepanska-Sadowska et al., 2018). It has been demonstrated that changes in the activity of the cerebral vasopressinergic system, principally AVP and V1aR, occur in the course of heart failure (Szczepanska-Sadowska et al., 2018; Reis et al., 2016). It has been shown that AVP by V1aR can play an important role in reducing body weight and in the regulation of metabolism (Aoyagi et al., 2009).

Based on the available studies, it can be assumed that the apelinergic and the vasopressinergic systems play a significant role in the pathogenesis of heart failure and in the regulation of metabolism. In addition, post-infarct heart failure (HF) and a high fat diet (HFD) have a significant impact on the activity of both the apelinergic and the vasopressinergic systems. Therefore, the aim of this study was to determine whether HF and HFD, applied separately or in combination, are associated with changes in the mRNA and protein expression of APJR, V1aR and V1bR in the brain, the heart and the adipose tissue of Sprague Dawley rats.

2. Materials and methods

Experiments were performed on 27 male 4-week-old Sprague Dawley rats, divided into the following groups: sham-operated rats on a normal fat diet (SO NFD; $n = 7$), sham-operated rats on a high fat diet (SO HFD; $n = 6$), post-infarct heart failure rats on a normal fat diet (HF NFD; n = 7), and post-infarct heart failure rats on a high fat diet (HF HFD, n = 7).

Our research was approved by the Second Local Animal Research Ethics Committee of the Medical University of Warsaw.

The rats were housed in individual cages under monitored conditions (temperature 22°–25 °C; humidity 40%–60%; 12-h light-dark cycle), food and water were available *ad libitum*. The rats were exposed during the 12 weeks to the following procedures (Fig. 1).

2.1. Feeding

The rats were fed with the high fat diet (HFD; contained: 31% fat, 17.1% protein, 35.5% carbohydrates, 0.18% sodium, and was 3842 kcal/kg; Labofeed B, Kcynia, Poland) during the whole study (12 weeks), starting from the 4th week of age. During the same time, the control rats were fed with the normal fat diet (NFD; contained: 3.6% fat, 17.4% protein, 60% carbohydrates, 0.2% sodium, and was 2864 kcal/kg; Labofeed B, Kcynia, Poland). Both diets have already been used by us in previous studies (Czarzasta et al., 2016; Czarzasta et al., 2018).

2.2. Post-infarct heart failure

The surgery was performed under general anesthesia (Ketamine 10 mg/100 g body wt i.p. (Vetoquinol), Xylazine 1 mg/100 g body wt i.p. (Vetoquinol)), using the procedure described by us previously (Cudnoch-Jedrzejewska et al., 2007; Czarzasta et al., 2016). Myocardial infarction was induced by permanent ligation of the left coronary artery with a suture thread (Ethicon 6.0).

The sham surgeries (SO) were similar as described above with the exception that the pericardium was only touched with a needle and the coronary artery was not ligated.

After surgery, the animals were placed in separate home cages and received an analgesic (Buprenorphine chloride 3 µg/100 g body wt i.p.; 5.95 nmol/ml, twice daily for 2–3 days) and an antibiotic (Penicillin, Polfa 10,000 IU/100 g body wt i.m.; 0.047 mmol/ml).

Four weeks were allowed for development of post-infarction HF in rats with coronary artery ligation (Cudnoch-Jedrzejewska et al., 2007; Pfeffer et al., 1979). The development of HF was biochemically confirmed by significantly increased plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) (Table 1).

2.3. Organs, tissue and blood sampling harvesting

At the end of the experiment, the animals were anesthetized by intraperitoneal administration of Ketamine (10 mg/100 g body wt i.p.) and Xylazine (1 mg/100 g body wt i.p.). Then, a 4 ml blood sample was taken from the right ventricle of the rats into tubes with EDTA as a coagulant in order to measure the plasma concentrations of apelin, copeptin and NT-proBNP.

Immediately after blood collection, the rats were euthanized by intraperitoneal injection of a lethal dose of Ketamine (300 mg/100 g body wt i.p.). After isolation of the brain, the hypothalamus was separated. After removing the cardiac atria, the left (LV) and right (RV) ventricles were separately collected, with the intraventricular septum remaining with the LV. In the rats with HF, the surface of the infarction was determined planimetrically (Leenen et al., 1999). The retroperitoneal adipose tissue was carefully collected in its entirety without blood vessels under evaluation with intraoperative microscope (SmartOptic, Seliga Microscopes). Tissue fragments were snap frozen in liquid nitrogen and then stored at −80 °C until analysis.

2.4. mRNA analysis (Real Time PCR; RT-PCR)

Fragments of the hypothalamus, LV and RV and the retroperitoneal

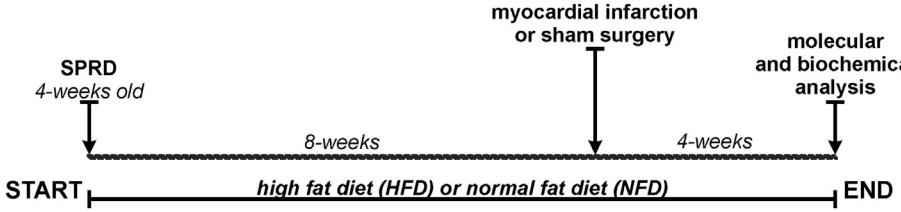

Fig. 1. Design of the study, showing implementation of the high fat diet or normal fat diet and myocardial infarction or sham surgery. HFD – high fat diet; NFD – normal fat diet; SPRD – Sprague Dawley rats.

Table 1
Characteristic of the animals.

Parameters	SO NFD (n = 7)	SO HFD (n = 6)	HF NFD (n = 7)	HF HFD (n = 7)
Body weight (g)	336.14 ± 1.78	302.83 ± 6.39	310.00 ± 15.08	339.86 ± 11.29
Infarction surface (%)			25.29 ± 0.75	44.57 ± 3.44$^{\$\$\$}$
NT-proBNP (pg/ml)	527 ± 26	524 ± 21	732 ± 37$^{\#\#\#}$	672 ± 21**
Left ventricle weight (g/100 g b.w.)	0.72 ± 0.01	0.69 ± 0.02	0.77 ± 0.05	0.81 ± 0.03**
Right ventricle weight (g/100 g b.w.)	0.18 ± 0.01	0.18 ± 0.02	0.41 ± 0.02$^{\#\#}$	0.39 ± 0.04*
Retroperitoneal adipose tissue weight (g/100 g b.w.)	3.37 ± 0.15	4.20 ± 0.18$^{\&}$	2.78 ± 0.09	4.62 ± 0.46$^{\$\$}$
Apelin-36 (ng/ml)	2.22 ± 0.03	2.27 ± 0.04	2.29 ± 0.03	2.29 ± 0.05
Copeptin (pg/ml)	223.29 ± 18.45	271.26 ± 50.13	434.19 ± 60.47$^{\#}$	568.55 ± 56.05**

SO NFD – sham-operated rats fed with the normal fat diet; SO HFD – sham-operated rats fed with the high fat diet; HF NFD – post-infarct heart failure rats fed with the normal fat diet; HF HFD – post-infarct heart failure rats fed with the high fat diet. * – significant difference between HF HFD and SO HFD rats; $^{\#}$ – significant difference between HF NFD and SO NFD rats; $^{\&}$ – significant difference between SO HFD and SO NFD; $^{\$}$ – significant difference between HF HFD and HF NFD. Significant differences were evaluated using one-way ANOVA with *post hoc* Tukey test for normal distributions and the ANOVA signed rank Kruskal-Wallis test with *post hoc* Dunn's test for non-parametric data. Means ± SE are shown. *$p < 0.05$; **$p < 0.01$; $^{\#}p < 0.05$; $^{\#\#}p < 0.01$; $^{\#\#\#}p < 0.001$; $^{\&}p < 0.05$; $^{\$\$}p < 0.01$; $^{\$\$\$}p < 0.001$.

adipose tissue were homogenized and the total RNA was extracted using a PureLink RNA Mini Kit (Ambion, Life Technologies). A multiplex Real Time PCR reaction was carried out in accordance with the Applied Biosystems protocols using the TaqMan® RNA-to-Ct™ 1-Step Kit, a primer for the target gene from Applied Biosystems (rat apelin receptor: gene symbol Aplnr, accession number Rn00580252_s1; vasopressin V1a receptor: gene symbol Avpr1a, accession number Rn00583910_m1; vasopressin V1b receptor: gene symbol Avpr1b, accession number Rn01490541_m1) labeled by reporter FAM dye, a primer for the housekeeping gene (rat GADPH: Applied Biosystems; gene symbol GAPDH, accession number Rn01775763_g1) labeled by VIC dye and RNA template in RNase-Free Water (Eppendorf). The amplification reaction was conducted in 40 cycles at 95 °C for 15 s and at 60 °C for 1 min. The RT-PCR reactions were performed in a ViiA™ 7 Real-Time PCR System thermocycler (Applied Biosystems). The relative gene expression was given on the basis of estimations of the values of the delta cycle threshold (ΔCt) by relative quantification to the endogenous control.

2.5. Protein analysis (Western Blot)

Fragments of the hypothalamus, LV, RV and the retroperitoneal adipose tissue were homogenized in a RIPA lysis buffer which contained: 10 mM Tris-HCl, pH 7.4; 100 mM NaCl; 1 mM EDTA; 1 mM EGTA; 1% Triton X-100; 10% glycerol; 0.1% SDS; 1 mM PMSF and peptidase inhibitors leupeptin and aprotinin (Halt™ Protease and Phosphatase Inhibitor Single-Use Cocktail, EDTA-Free, Thermo Fisher). Samples containing 10 μg/μl of total protein were separated on 8% SDS-polyacrylamide gels. Separated proteins were transferred into PVDF membranes (Trans-Blot® Turbo™ RTA Mini PVDF Transfer Kit; Bio-Rad) by using the Trans-Blot® Turbo™ Transfer System (Bio-Rad). The PVDF membranes were incubated for 1 h with: a primary rabbit polyclonal antibody against APJR (1:200 dilution, sc-33823; Santa Cruz Biotechnology), a primary rabbit polyclonal antibody against V1aR (1:200 dilution, sc-30025; Santa Cruz Biotechnology), a primary goat polyclonal antibody against V1bR (1:200 dilution, sc-18,105; Santa Cruz Biotechnology), and a secondary antibody: goat anti-rabbit conjugated to Horseradish Peroxidase (HRP) (1:2000, sc-2004; Santa Cruz Biotechnology), a secondary antibody: rabbit anti-goat conjugated to HRP (1:2000, sc-2768; Santa Cruz Biotechnology). For loading control, the blots were stripped and reprobed for rabbit polyclonal to anti-β Actin antibody (1:1000dilution, ab8227; Abcam) and goat anti-rabbit secondary antibody, conjugated to HRP (1:2000, sc-2004; Santa Cruz Biotechnology). The specific bands were visualized with the colorimetric method by Amplified Opti-4CN Substrate Kit (Bio-Rad), and quantified by densitometry using a ChemiDoc Imaging Systems (ChemiDoc™ MP System, Bio-Rad). APJR, V1aR and V1bR protein expressions were normalized with β-actin to control for the amount of protein loading and protein transfer and expressed as a relative ratio.

2.6. Plasma apelin, copeptin and NT-proBNP measurements (ELISA)

Apelin-36, copeptin and NT-proBNP plasma concentrations were checked using enzyme-linked immunoassays (ELISA): (Apelin-36 (Rat, Mouse) - EIA Kit, extraction-free, EK-057-28, Phoenix Pharmaceuticals, Inc.; Rat Vasopressin-neurophysin 2-copeptin ELISA Kit, Wuhan EIAab Science Co.; Rat (NT-proBNP) ELISA Kit, 201-11-0068, Shanghai Sunred Biological Technology Co.). Each ELISA test was carried out in accordance with the instructions provided by the manufacturer.

2.7. Statistics

Comparisons of the mean values of each characteristic were made using one-way ANOVA with *post hoc* Tukey test for normal distributions and the ANOVA signed rank Kruskal-Wallis test with *post hoc* Dunn's test for non-parametric data. The differences were considered statistically significant if $p < 0.05$. All values presented in the text, tables and figures are expressed as means ± standard errors (SE). Statistical analysis was performed using Statistica software (version 13).

3. Results

3.1. Characteristics of the animals

One-way ANOVA revealed significant differences in the body weight between the examined groups of rats [$F(3.23) = 3.215$, $p < 0.05$], whereas individual comparisons by *post hoc* Tukey test showed a lack of significant differences in body weight (Table 1).

Significant differences were found between the infarction surface of the groups ($p < 0.001$; Kruskal-Wallis test). The infarction surface was significantly higher in the HF HFD rats in comparison with the HF NFD rats ($p < 0.001$) (Table 1).

One-way ANOVA indicated significant differences in plasma NT-proBNP concentrations [$F(3.23) = 15.058$, $p < 0.001$]. Furthermore plasma NT-proBNP concentrations were significantly higher in the rats with HF on the HFD as well as on the NFD in comparison with the SO rats maintained on both types of diet respectively (HF HFD *vs* SO HFD, $p < 0.01$; HF NFD *vs* SO NFD, $p < 0.001$) (Table 1).

There were no significant differences in the LV weight between the groups of rats. The *post hoc* Tukey test showed that LV weight was significantly higher in the HF HFD rats compared with the SO HFD rats ($p < 0.01$) (Table 1).

Significant differences between the groups were found in the weights of the RV ($p < 0.001$; Kruskal-Wallis test). Moreover, significantly higher RV weight was found in the HF rats maintained on both the HFD and the NFD than in the sham-operated rats on both types

of diet (HF HFD *vs* SO HFD, $p < 0.05$; HF NFD *vs* SO NFD, $p < 0.01$) (Table 1).

Significant differences were found between the retroperitoneal adipose tissue weights of the groups ($p < 0.01$; Kruskal-Wallis test). Individual comparisons demonstrated significant differences in the retroperitoneal adipose tissue weight observed in rats on the HFD with post-infarct heart failure and sham-operated rats in comparison with the rats on the NFD with HF or SO, respectively (HF HFD *vs* HF NFD, $p < 0.01$; SO HFD *vs* SO NFD, $p < 0.05$) (Table 1).

3.2. Plasma apelin and copeptin concentrations

There were no significant differences in the plasma apelin-36 concentration between all groups of rats (Table 1).

One-way ANOVA revealed significant differences in the plasma copeptin concentrations [$F(3.22) = 9.628$, $p < 0.001$], whereas *post hoc* Tukey test showed that the plasma concentration of copeptin was significantly higher in the rats with HF maintained on the HFD or the NFD in comparison with the SO rats on both types of diet (HF HFD *vs* SO HFD, $p < 0.01$; HF NFD *vs* SO NFD, $p < 0.05$) (Table 1).

3.3. mRNA expression and protein levels of APJR, V1aR and V1bR in the hypothalamus

Significant differences between the groups of rats were found with regard to the expression of APJR mRNA ($p < 0.01$; Kruskal-Wallis test) as well as the protein APJR level in the hypothalamus [$F(3.17 = 11.297$, $p < 0.001$; One-way ANOVA]. APJR mRNA expression was significantly higher in the SO NFD rats than in the HF NFD rats ($p < 0.001$) (Fig. 2A), whereas the APJR protein level was significantly higher in the SO HFD rats in comparison with the SO NFD rats ($p < 0.001$) and in comparison with the HF HFD ($p < 0.05$) (Fig. 2B).

There were no significant differences in the V1aR and V1bR mRNA expression in the hypothalamus among the groups (Fig. 2C and Fig. 2E), whereas the V1aR protein level in the hypothalamus was significantly higher in the HF NFD rats compared with the HF HFD rats ($p < 0.05$) (Fig. 2D) and the V1bR protein level was significantly higher in the SO NFD rats compared with the HF NFD rats ($p < 0.05$) (Fig. 2F).

3.4. mRNA expression and protein levels of APJR, V1aR and V1bR in the left ventricle

Significant differences between the groups of rats were found with regard to the mRNA expression of APJR in the LV ($p < 0.001$; Kruskal-Wallis test). Additionally, HFD significantly increased the expression of APJR mRNA in both SO and HF groups in comparison with groups on NFD (HF HFD *vs* HF NFD, $p < 0.05$; SO HFD *vs* SO NFD, $p < 0.05$) (Fig. 3A), whereas HF had no effect on APJR mRNA expression and there were no significant differences in the APJR protein level between the examined groups of rats (Fig. 3B).

One-way ANOVA revealed significant differences in V1aR mRNA expression in LV between all groups of rats [$F(3.19) = 14.503$, $p < 0.001$]. Furthermore, the expression of V1aR mRNA was significantly higher in the sham-operated rats maintained on the HFD or the NFD, compared with the rats with post-infarct heart failure on both types of diet (SO NFD *vs* HF NFD, $p < 0.001$; SO HFD *vs* HF HFD, $p < 0.05$) (Fig. 3C). Significant differences between the groups of rats were found with regard to the V1aR protein level between the all groups of rats ($p < 0.01$; Kruskal-Wallis test), whereas *post hoc* Dunn's test showed that the protein level of V1aR was significantly higher in the HF HFD rats than in the HF NFD rats ($p < 0.01$), and in comparison with the SO HFD rats ($p < 0.01$) (Fig. 3D).

There were no significant differences in the expression of V1bR mRNA in the LV between all groups (Fig. 3E). However, significant differences between the groups of rats were found in the V1bR protein level in the LV ($p < 0.001$; Kruskal-Wallis test) The V1bR protein level was significantly higher in the HF HFD rats in comparison with the HF NFD rats ($p < 0.01$) and compared with the SO HFD rats ($p < 0.01$) (Fig. 3F).

3.5. mRNA expression and protein levels of APJR, V1aR and V1bR in the right ventricle

Significant differences were found with regard to the expression in the mRNA expression ($p < 0.01$; Kruskal-Wallis test) and protein level [$F(3.210 = 56.252$, $p < 0.001$; One-way ANOVA] of APJR in the RV between all groups of rats. APJR mRNA expression in the RV was significantly higher in the rats maintained on the HFD with HF or SO in comparison with the rats on NFD, with HF as well as SO (HF HFD *vs* HF NFD, $p < 0.05$; SO HFD *vs* SO NFD, $p < 0.05$) (Fig. 4A). Whereas the APJR protein level was significantly lower in the rats with HF on the HFD or the NFD, compared with the SO rats maintained on the HFD or the NFD (HF HFD *vs* SO HFD, $p < 0.001$; HF NFD *vs* SO NFD, $p < 0.001$) (Fig. 4B).

Significant differences were found in the V1aR mRNA expression ($p < 0.05$; Kruskal-Wallis test) and protein level [$F(3.22) = 4.653$, $p < 0.05$; One-way ANOVA] of V1aR in the RV between all groups of rats. The V1aR mRNA expression in the RV was significantly higher in the SO HFD rats than in the HF HFD rats ($p < 0.05$) and compared with the SO NFD rats ($p < 0.01$) (Fig. 4C). Similarly, the protein level of V1aR was significantly higher in the SO HFD rats in comparison with the SO NFD rats ($p < 0.05$) (Fig. 4D).

One-way ANOVA showed no significant differences in the mRNA V1bR expression in the RV between all groups, whereas *post hoc* Tukey test showed that the V1bR mRNA expression in the RV was significantly higher in the HF HFD rats in comparison with the HF NFD ($p < 0.05$) and compared with the SO HFD rats ($p < 0.05$) (Fig. 4E). However, the V1bR protein level was significantly different between the groups [$F(3.21) = 35.286$, $p < 0.001$; One-way ANOVA] and the V1bR protein level was significantly higher in the HF HFD rats than in the HF NFD rats ($p < 0.001$), and higher than in the SO HFD rats ($p < 0.001$). The V1bR protein level was significantly higher in the SO NFD rats compared with the SO HFD rats ($p < 0.001$) and in comparison with the HF NFD rats ($p < 0.001$) (Fig. 4F).

3.6. mRNA expression and protein levels of APJR, V1aR and V1bR in the retroperitoneal adipose tissue

One-way ANOVA revealed significant differences in the mRNA expression [$F(3.160 = 15.202$, $p < 0.001$] and protein level ($p < 0.001$; Kruskal-Wallis test) of APJR in the retroperitoneal adipose tissue between all groups of rats. The APJR mRNA expression was significantly higher in the HF NFD rats in comparison with the HF HFD rats ($p < 0.05$) and compared with the SO NFD rats ($p < 0.001$) (Fig. 5A), whereas the protein level of APJR was significantly higher in the HF HFD rats than in the HF NFD rats ($p < 0.05$) and in comparison with the SO HFD rats ($p < 0.01$). The APJR protein level was also significantly higher in the SO NFD rats in comparison with the SO HFD ($p < 0.01$) and compared with the HF NFD ($p < 0.05$) (Fig. 5B).

There were no significant differences in the expression of V1aR and V1bR mRNA expressions in the retroperitoneal adipose tissue (Fig. 5C, E), whereas there were significant differences in V1aR [$F(3.18) = 28.677$, $p < 0.001$; One-way ANOVA] and V1bR [$F(3.18) = 19.876$, $p < 0.001$; One-way ANOVA] protein levels between all groups of rats. Moreover, *post hoc* Tukey test demonstrated that the V1aR protein level was significantly higher in the SO NFD rats in comparison with the SO HFD rats ($p < 0.001$) and compared with the HF NFD rats ($p < 0.001$). It was also significantly higher in the HF HFD rats compared with the HF NFD rats ($p < 0.001$) and compared with the SO HFD rats ($p < 0.001$) (Fig. 5D), whereas the V1bR protein level was significantly higher in the SO HFD rats than in the HF HFD rats ($p < 0.001$) and in comparison with the SO NFD rats ($p < 0.001$)

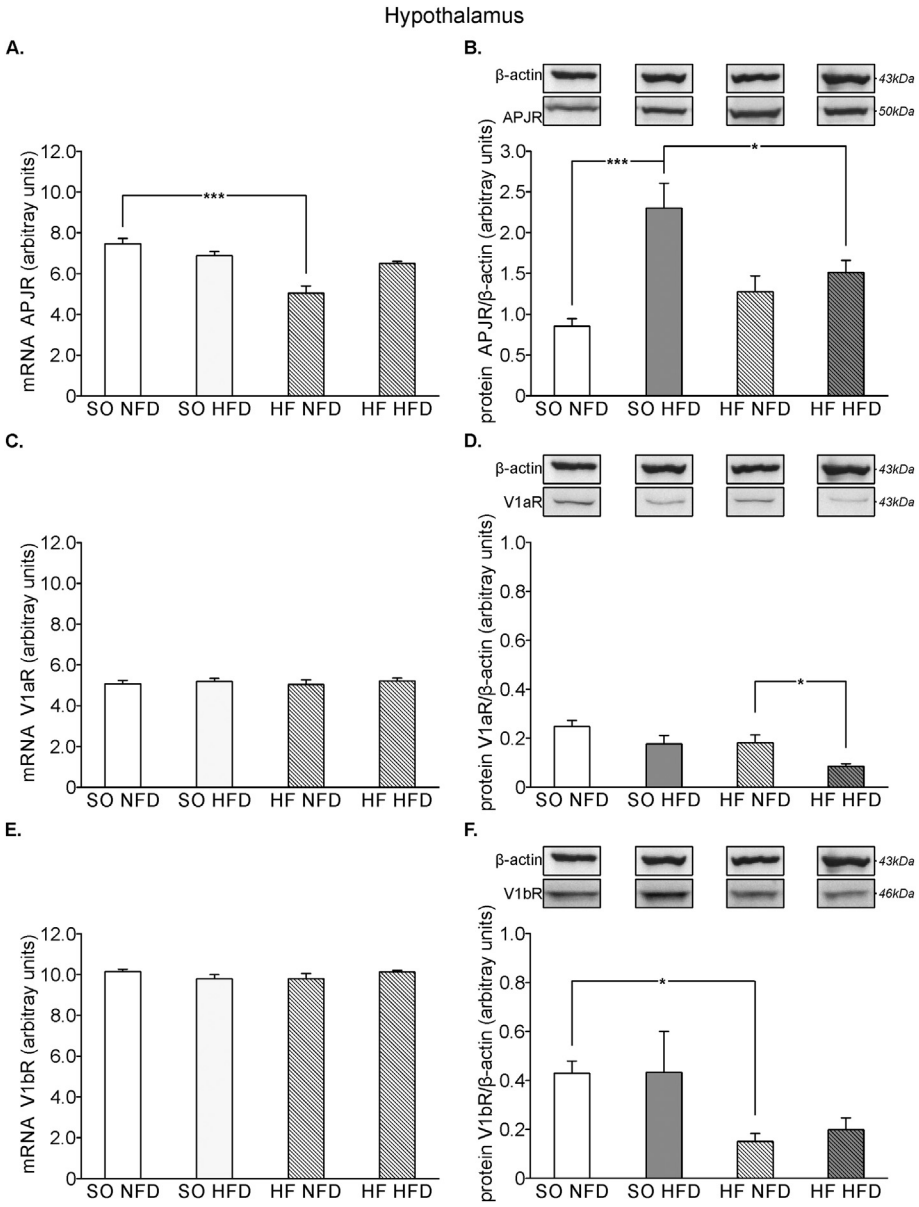

Fig. 2. A. APJ receptor mRNA expression in the hypothalamus in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. mRNA APJR – apelin receptor mRNA expression; SO NFD – sham-operated rats fed with the normal fat diet; SO HFD – sham-operated rats fed with the high fat diet; HF NFD – post-infarct heart failure rats fed with the normal fat diet; HF HFD – post-infarct heart failure rats fed with the high fat diet. Significant differences were evaluated using the ANOVA signed rank Kruskal-Wallis test with *post hoc* Dunn's test. Means ± SE are shown; ***p < 0.001.
B. APJ receptor protein level in the hypothalamus in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. Protein APJR – apelin receptor protein level. Other abbreviations as in A. Significant differences were evaluated using one-way ANOVA with *post hoc* Tukey test. Means ± SE are shown; *p < 0.05; ***p < 0.001.
C. V1a vasopressin receptor mRNA expression in the hypothalamus in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. mRNA V1aR – V1a vasopressin receptor mRNA expression. Other abbreviations as in A.
D. V1a vasopressin receptor protein level in the hypothalamus in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. Protein V1aR – V1a vasopressin receptor protein level. Other abbreviations as in A. Significant differences were evaluated using the ANOVA signed rank Kruskal-Wallis test with *post hoc* Dunn's test. Means ± SE are shown; *p < 0.05.
E. V1b vasopressin receptor mRNA expression in the hypothalamus in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. mRNA V1bR – V1b vasopressin receptor mRNA expression. Other abbreviations as in A.
F. V1b vasopressin receptor protein level in the hypothalamus in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. Protein V1bR – V1b vasopressin receptor protein level. Other abbreviations as in A. Significant differences were evaluated using the ANOVA signed rank Kruskal-Wallis test with *post hoc* Dunn's test. Means ± SE are shown; *p < 0.05.

(Fig. 5F).

4. Discussion

The main finding of our study is that post-infarct heart failure and a high fat diet differentially affect the expression of mRNA and protein levels of the APJR and the V1aR and V1bR in the hypothalamus, in the left and the right ventricles and in the retroperitoneal adipose tissue. The observed differences between mRNA expression and the translation efficiency suggest transcription-independent regulation of translation due to the epigenetic imprinting of mRNA (Slobodin et al., 2017) or other mechanisms (Miranda and Jones, 2007; Cenik et al., 2015).

The hypothalamus is a structure of the CNS in which the key centers are located, both for the regulation of hunger and satiety, as well as the regulation of the cardiovascular system function (Szczepanska-Sadowska et al., 2010). However, as the presented studies indicate, the above processes can be modified by the type of diet and by the presence of pathology of the cardiovascular system both of which affect the expression of receptors of different peptides such as apelin and vasopressin.

On the basis of the presented results, it can be assumed that the main factor influencing APJR mRNA expression in the hypothalamus was HF. However, in the regulation of the APJR protein level, the HFD played a key role, whereas the combination of a HF with HFD reduced the APJR protein level in the hypothalamus. Similarly, our previous studies showed that HF had greater influence than a HFD on APJR mRNA expression in the hypothalamus (Czarzasta et al., 2016). In contrast, Clarke et al. (2009) reported that DIO (diet-induced obese) rats on a HFD showed an increase in APJR mRNA expression in the hypothalamus. Reaux-Le Goazigo et al. (2011) also showed a significantly higher expression of APJR mRNA in the hypothalamus in db/db mice and in Zucker rats on a HFD compared with animals on a NFD. The differences in APJR mRNA expression for HF and a HFD may have resulted from a different activation of transcription factors such as SP1 (specificity protein 1) (Hata et al., 2007), whereas, probably, the translation of APJR in the hypothalamus in SO NFD rats was affected by

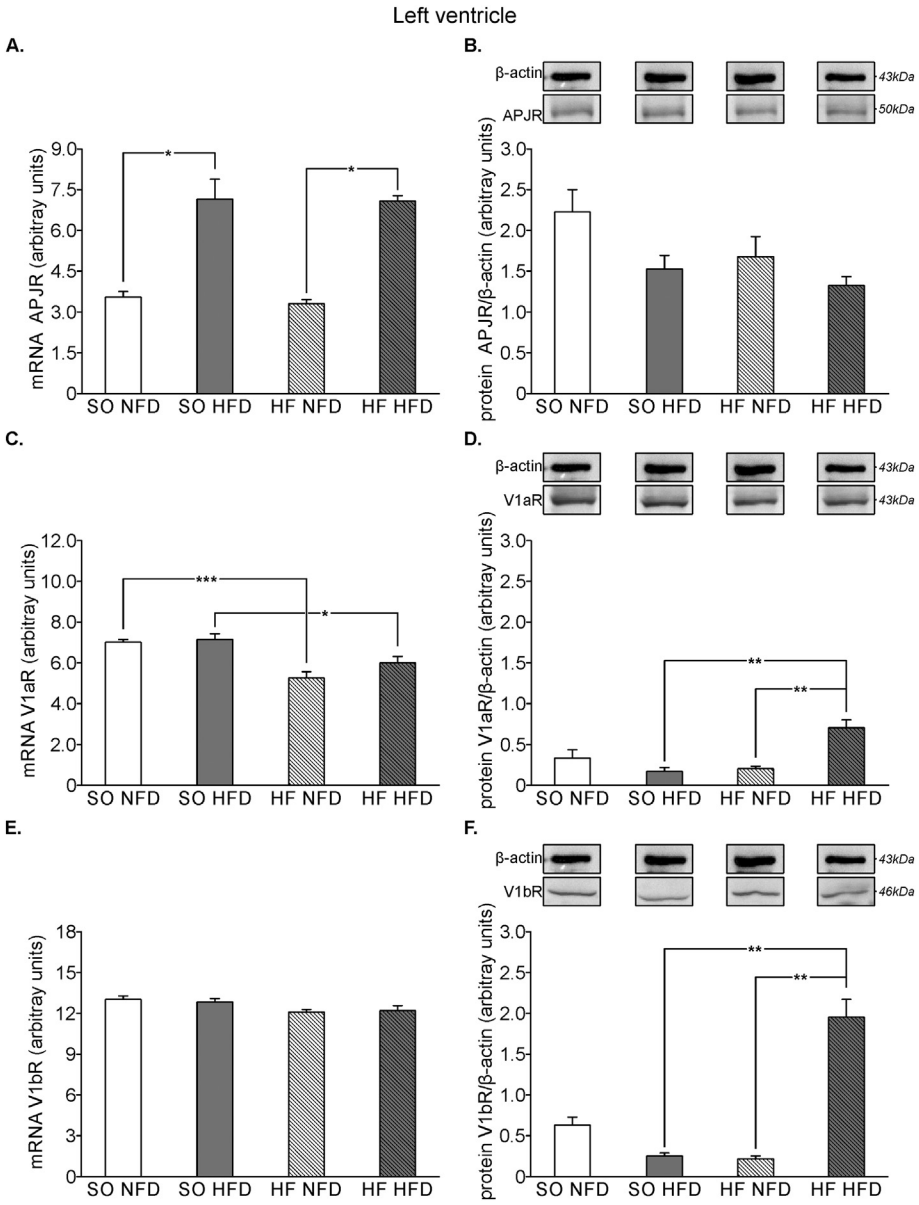

Fig. 3. A. APJ receptor mRNA expression in the left ventricle in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. mRNA APJR – apelin receptor mRNA expression; SO NFD – sham-operated rats fed with the normal fat diet; SO HFD – sham-operated rats fed with the high fat diet; HF NFD – post-infarct heart failure rats fed with the normal fat diet; HF HFD – post-infarct heart failure rats fed with the high fat diet. Significant differences were evaluated using the ANOVA signed rank Kruskal-Wallis test with *post hoc* Dunn's test. Means ± SE are shown; *$p < 0.05$.

B. APJ receptor protein level in the left ventricle in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. Protein APJR – apelin receptor protein level. Other abbreviations as in A.

C. V1a vasopressin receptor mRNA expression in the left ventricle in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. mRNA V1aR – V1a vasopressin receptor mRNA expression. Other abbreviations as in A. Significant differences were evaluated using one-way ANOVA with *post hoc* Tukey test. Means ± SE are shown; *$p < 0.05$; ***$p < 0.001$.

D. V1a vasopressin receptor protein level in the left ventricle in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. Protein V1aR – V1a vasopressin receptor protein level. Significant differences were evaluated using the ANOVA signed rank Kruskal-Wallis test with *post hoc* Dunn's test. Other abbreviations as in A. Means ± SE are shown; **$p < 0.01$.

E. V1b vasopressin receptor mRNA expression in the left ventricle in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. mRNA V1bR – V1b vasopressin receptor mRNA expression. Other abbreviations as in A.

F. V1b vasopressin receptor protein level in the left ventricle in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. Protein V1bR – V1b vasopressin receptor protein level. Other abbreviations as in A. Significant differences were evaluated using the ANOVA signed rank Kruskal-Wallis test with *post hoc* Dunn's test. Means ± SE are shown; **$p < 0.01$.

insulin, the levels of which are elevated in HFD rats (Boucher et al., 2005; Cudnoch-Jedrzejewska et al., 2015).

The observed changes of receptor expression level have systemic effects. It was shown that apelin synthesized in the CNS may cause an increase in hemodynamic parameters in rats on a NFD (Kagiyama et al., 2005; Zhang et al., 2009; Cudnoch-Jedrzejewska et al., 2015; Czarzasta et al., 2016). In contrast, in rats with HF and/or HFD, apelin did not cause a pressure effect (Cudnoch-Jedrzejewska et al., 2015; Czarzasta et al., 2016). A likely reason for the abolition of the pressor effect could be due to the influence of HFD on APJR inactivation in the CNS (Clarke et al., 2009).

It is thought that the central influence of apelin on the regulation of cardiovascular function can be mediated *via* V1aR (Griffiths et al., 2017). These assumptions seem to confirm our preliminary results in which the intraventricular infusion of the V1aR antagonist (V1aRANT; [deamino-Pen1, O-Me-Tyr2, Arg8]-Vasopressin) caused the abolition of the pressure effect of apelin-13 in Sprague Dawley rats on NFD (Borowik et al., 2014).

Our study showed no significant differences in V1aR mRNA expression in the hypothalamus between all groups. In contrast, the V1aR protein level was significantly higher in HF NFD rats, and the HFD caused a decrease in the V1aR protein level in rats with HF. In the animal model of myocardial hypertrophy and LV dysfunction and the model of supravalvular aortic stenosis, it was shown that V1aR expression in the medulla oblongata was significantly higher (Muders et al., 2002). Based on the available data, it can be assumed that the increase in the V1aR protein level in HF NFD rats in the hypothalamus could be caused by increased synthesis and release of vasopressin from PVN and SON neurons. It has been proven that HF leads to an increase in AVP blood concentration, in proportion to the stage of heart failure (Reis et al., 2016; Vishram-Nielsen and Gustafsson, 2017). In the present study, the increased secretion of vasopressinergic system activity was confirmed by an increase in copeptin plasma concentration, which is considered to be the equivalent of AVP (Ettema et al., 2017). In our

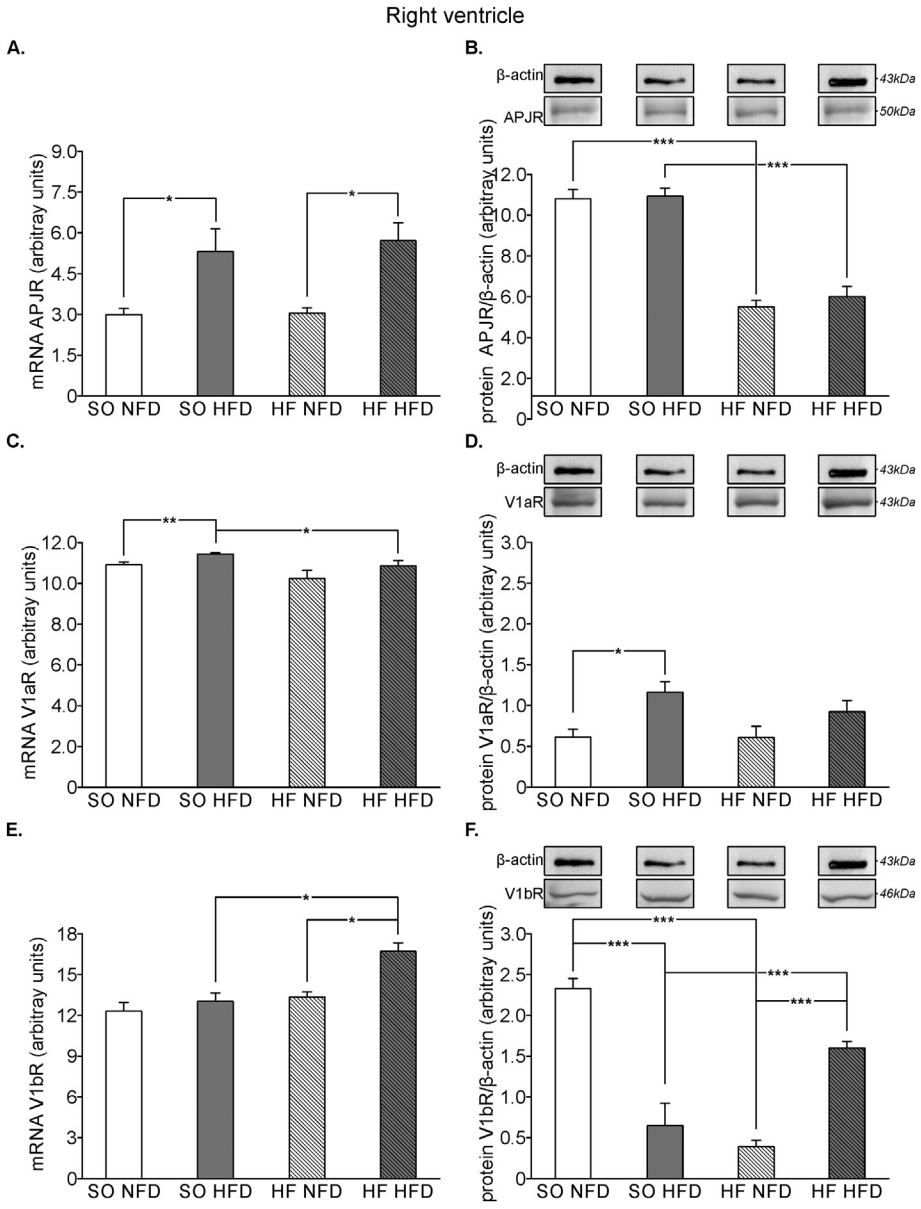

Fig. 4. A. APJ receptor mRNA expression in the right ventricle in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. mRNA APJR – apelin receptor mRNA expression; SO NFD – sham-operated rats fed with the normal fat diet; SO HFD – sham-operated rats fed with the high fat diet; HF NFD – post-infarct heart failure rats fed with the normal fat diet; HF HFD – post-infarct heart failure rats fed with the high fat diet. Significant differences were evaluated using the ANOVA signed rank Kruskal-Wallis test with *post hoc* Dunn's test. Means ± SE are shown; *p < 0.05.

B. APJ receptor protein level in the right ventricle in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. Protein APJR – apelin receptor protein level. Other abbreviations as in A. Significant differences were evaluated using one-way ANOVA with *post hoc* Tukey test. Means ± SE are shown; ***p < 0.001.

C. V1a vasopressin receptor mRNA expression in the right ventricle in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. mRNA V1aR – V1a vasopressin receptor mRNA expression. Other abbreviations as in A. Significant differences were evaluated using the ANOVA signed rank Kruskal-Wallis test with *post hoc* Dunn's test. Means ± SE are shown; *p < .05; **p < 0.01.

D. V1a vasopressin receptor protein level in the right ventricle in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. Protein V1aR – V1a vasopressin receptor protein level. Other abbreviations as in A. Significant differences were evaluated using one-way ANOVA with *post hoc* Tukey test. Means ± SE are shown; *p < 0.05.

E. V1b vasopressin receptor mRNA expression in the right ventricle in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. mRNA V1bR – V1b vasopressin receptor mRNA expression. Significant differences were evaluated using one-way ANOVA with *post hoc* Tukey test. Other abbreviations as in A. Means ± SE are shown; *p < 0.05.

F. V1b vasopressin receptor protein level in the right ventricle in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. Protein V1bR – V1b vasopressin receptor protein level. Other abbreviations as in A. Significant differences were evaluated using one-way ANOVA with *post hoc* Tukey test. Means ± SE are shown; ***p < 0.001.

study, plasma concentration of copeptin was significantly higher in rats with HF both on the HFD and on the NFD compared with rats undergoing SO on both types of diet. Recently, high expectations are associated with copeptin as a biomarker in HF (Balling et al., 2018; Parizadeh et al., 2018). Additionally, research by Enhörning et al. (2013) showed that the measurement of plasma concentration of copeptin can be used as an independent indicator that predicts the development of type 2 diabetes and abdominal obesity, but unfortunately not the development of metabolic syndrome. It has been described that increased AVP secretion in HF is the main cause of hyponatremia with its negative effects on the whole organism, including the CNS function (Vishram-Nielsen and Gustafsson, 2017). Available data have shown that vasopressin and apelin have an antagonistic effect on the regulation of body fluids and osmotic homeostasis (Urwyler et al., 2016).

The major vasopressinergic receptor involved in central regulation of the cardiovascular system is the V1aR (Griffiths et al., 2017; Szczepanska-Sadowska et al., 2018; Yang et al., 2019), but another AVP receptor is present mainly in the CNS, namely, V1bR in circulatory regions such as the PVN in the hypothalamus (Szczepanska-Sadowska et al., 2018). Current research has also shown that in HF there is also a decrease in the V1bR protein level in the hypothalamus with the high fat diet appearing to have no effect on V1bR expression. Numerous studies have shown that stress is the main regulator of the expression of V1bR in the CNS (Goncharova et al., 2018). Single clinical studies indicate that HF may be accompanied by increased secretion of stress hormones such as ACTH and cortisol (Güder et al., 2015). Based on the available data, we suppose that the lowering of the V1bR protein level in the HF NFD rats is caused by the process of “downregulation” of the receptors due to a stimulating factor, which in rats with HF could be corticosterone, and the increase of the V1bR protein level in the HF NFD rats is accompanied by the anhedonia symptom observed during chronic HF (Cudnoch-Jedrzejewska et al., 2014; Goncharova et al., 2018).

Available data show that particularly important for the development of cardiovascular disease is excessive proliferation of adipose tissue in the abdominal area, leading to the development of so-called

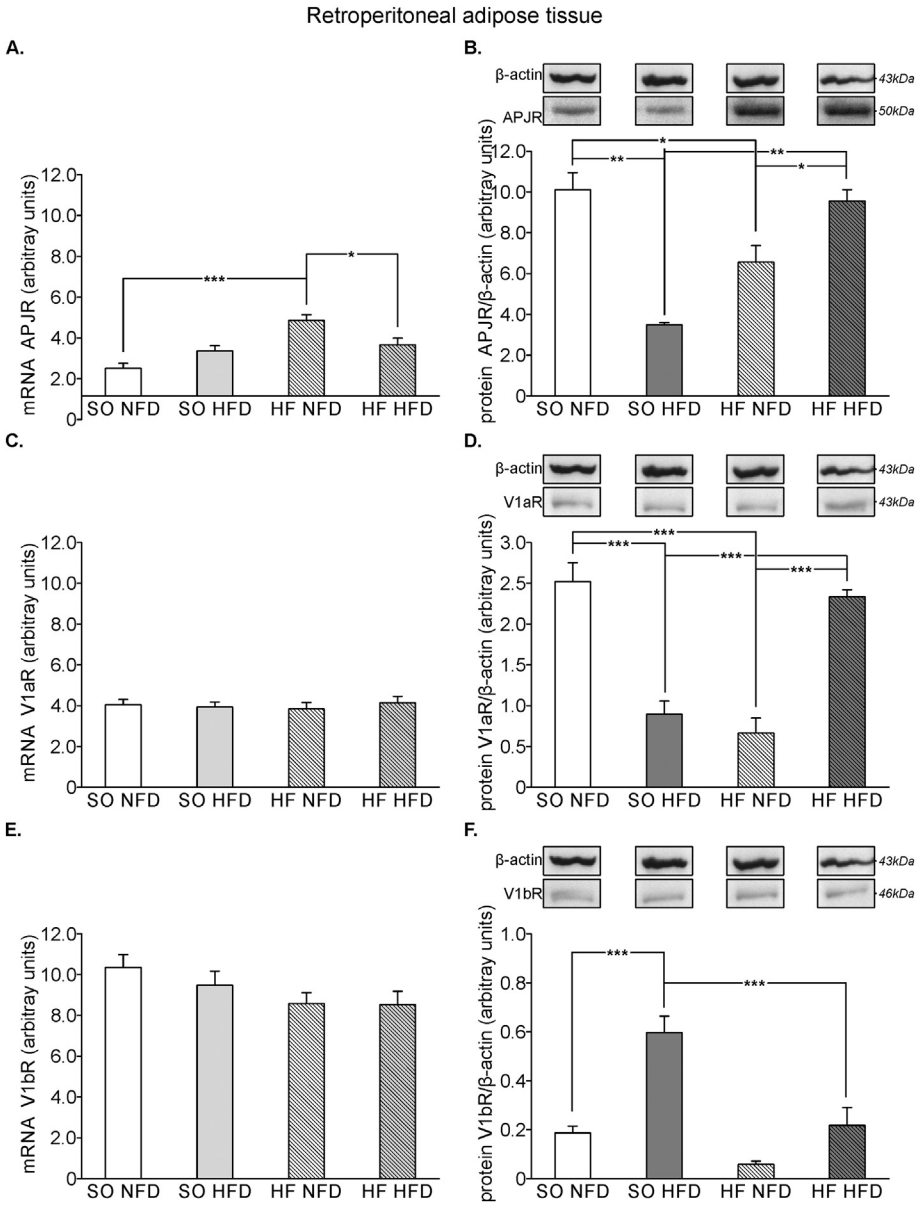

Fig. 5. A. APJ receptor mRNA expression in the retroperitoneal adipose tissue in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. mRNA APJR – apelin receptor mRNA expression; SO NFD – sham-operated rats fed with the normal fat diet; SO HFD – sham-operated rats fed with the high fat diet; HF NFD – post-infarct heart failure rats fed with the normal fat diet; HF HFD –post-infarct heart failure rats fed with the high fat diet. Significant differences were evaluated using one-way ANOVA with *post hoc* Tukey test. Means ± SE are shown; *p < 0.05; ***p < 0.001.
B. APJ receptor protein level in the retroperitoneal adipose tissue in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. Protein APJR – apelin receptor protein level. Other abbreviations as in A. Significant differences were evaluated using the ANOVA signed rank Kruskal-Wallis test with *post hoc* Dunn's test. Means ± SE are shown; *p < 0.05; **p < 0.01.
C. V1a vasopressin receptor mRNA expression in the retroperitoneal adipose tissue in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. mRNA V1aR – V1a vasopressin receptor mRNA expression. Other abbreviations as in A.
D. V1a vasopressin receptor protein level in the retroperitoneal adipose tissue in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. Protein V1aR – V1a vasopressin receptor protein level. Other abbreviations as in A. Significant differences were evaluated using one-way ANOVA with *post hoc* Tukey test. Means ± SE are shown; ***p < 0.001.
E. V1b vasopressin receptor mRNA expression in the retroperitoneal adipose tissue in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. mRNA V1bR – V1b vasopressin receptor mRNA expression. Other abbreviations as in A.
F. V1b vasopressin receptor protein level in the retroperitoneal adipose tissue in the sham-operated rats fed with the normal fat or high fat diet and in the post-infarct heart failure rats fed with the normal fat or high fat diet. Protein V1bR – V1b vasopressin receptor protein level. Other abbreviations as in A. Significant differences were evaluated using one-way ANOVA with *post hoc* Tukey test. Means ± SE are shown; ***p < 0.001.

abdominal obesity (Smith, 2015). In animal models of obesity, the equivalent of abdominal obesity is excessive proliferation of visceral adipose tissue, to which retroperitoneal adipose tissue belongs (Hariri and Thibault, 2010). In the present study, no differences in body weight between rats from individual groups were found, but retroperitoneal adipose tissue weight was significantly higher in rats on HFD compared with NFD rats, both those who developed HF and those treated with SO. It is known that adipose tissue is the main location of apelin synthesis (Boucher et al., 2005). Apelin synthesized in adipose tissue undergoes secretion to the circulation system (Bertrand et al., 2015). In our study, the concentration of apelin-36 was similar between all groups of rats. Many years of research have ruled out the possibility of using apelin as a biomarker for HF (Földes et al., 2003; Francia et al., 2007; Weir et al., 2009). Similarly, significant fluctuations in plasma apelin concentration depending on dyslipidemia and insulin resistance in obese patients were observed (Boucher et al., 2005; Soriguer et al., 2009).

In the present study, APJR mRNA expression in the retroperitoneal adipose tissue was regulated mainly by HF. The APJR protein level in the retroperitoneal adipose tissue was also influenced by HF and by HFD as well. Wu et al. (2014) found that HFD can reduce the expression of APJR mRNA in adipose tissue. On the basis of the obtained results, it can be assumed that the increased mass of retroperitoneal adipose tissue, which was accompanied by an increase in APJR protein expression, was associated with the need to store larger energy deposits in the form of fat in adipose tissue in HF HFD rats. It has been shown that the main energetic substrate for the myocardium are free fatty acids derived from the β-oxidation of lipids from adipose tissue (Dirkx et al., 2011).

Based on the available data, it can be concluded that both apelin *via* APJR and AVP *via* V1aR can inhibit adipose tissue proliferation in

C57BL/6 mice and adipose-derived stem cells (hASCs) (Higuchi et al., 2007; Tran et al., 2015). In the presented studies, there were no significant differences in the mRNA expressions of V1aR and V1bR in the retroperitoneal adipose tissue between all rat groups. While HFD significantly decreased V1aR protein levels in SO rats, the combination of HFD and HF caused an increase in V1aR protein level in retroperitoneal adipose tissue. However, V1bR protein levels were significantly higher in SO HFD rats. The available data indicate that the expression of V1aR in adipose tissue occurs very early in fetal life and plays an important role in adipocytogenesis (Tran et al., 2016). It has also been demonstrated that AVP *via* V1aR affects metabolism. Studies in mice with the V1aR knockout showed an increase in lipid metabolism, muscle proteolysis and suppression of insulin signaling, which was supported by impaired glucose tolerance (Aoyagi et al., 2009). In addition, studies in V1aR knockout mice and studies on patients with a V1aR mutation showed a tendency to develop obesity and type 2 diabetes (Aoyagi et al., 2009; Enhörning et al., 2009).

Based on the available data, it can be assumed that the V1bR in adipose tissue mediates the lipids and glucose metabolism. Studies on V1bR knockout mice (V1bR−/−) showed a change in glucose metabolism in adipose tissue, whereas the lipolysis process did not change (Fujiwara et al., 2007). Hiroyama et al. (2009) found a higher weight of epididymal adipose tissue in V1bR−/− mice, decreased lipolysis and increased lipogenesis. In our study, increased expression of V1bR in SO HFD was accompanied by an increase in the weight of the retroperitoneal adipose tissue, which may indicate that AVP *via* V1bR can affect the stimulation of adipose tissue proliferation and lipogenesis.

Obesity, resulting from central disorders of hunger and satiety regulation leading to excessive proliferation of adipose tissue, is a direct predictor of the development of cardiovascular diseases including myocardial infarction and HF (Ortega et al., 2016). In this study, HF was developed by ligation of the left coronary artery in rats who survived for four weeks after surgery, which is a recognized method of HF in rats (Pfeffer et al., 1979; Råmunddal et al., 2006). The development of HF in our study was confirmed by the measurement of plasma NT-proBNP concentration, which was significantly higher in HF rats, both on HFD and NFD compared with SO rats on NFD and HFD respectively. Additionally, we observed a larger infarct area in HF HFD rats in comparison with HF NFD rats. Perhaps a larger infarct area in HF HFD rats compared with HF NFD rats could be due to the increased myocardial fibrosis caused by HFD (Czarzasta et al., 2018). Based on the results obtained, it can be assumed that greater activation of fibrinogen, collagen and extracellular matrix factors may increase post-infarction necrosis in HFD, which can change the apelinergic and vasopressinergic system activity and may have a different effect on the myocardial function in HF conditions (Folino et al., 2015; Chen et al., 2015).

In our study, APJR mRNA expression in both the LV and RV appeared to be largely regulated by HFD. In contrast, the APJR protein level in the LV was not significantly different between all groups of rats, whereas the APJR protein level in the RV was significantly lower in rats with HF on both the HFD and the NFD compared with SO rats on both types of diet. There is one study about the mRNA expression and protein level of APJR in the RV. Falcão-Pires et al. (2009) showed that apelin affects the reduction of the RV load in rats with pulmonary hypertension. In our study, the RV weight was significantly higher in rats with HF on both types of diet compared with the SO rats, probably because of the RV overload. The available literature pays more attention to the expression of APJR in the LV. Research on rats with myocardial infarction, performed by ligation of the left coronary artery (similar to our study), showed an increase in APJR mRNA expression in cardiomyocytes during the first 24 h after the induction of pathology (Ronkainen et al., 2007). Similarly, in mice with left coronary artery ligation, an increase in the activity of the apelin/APJR pathway in the myocardium has already been observed in the early period of HF (Sheikh et al., 2008). It was found that the level of the APJR protein in the myocardium during HF could increase or remain unchanged, in accordance with the New York Heart Association (NYHA) functional classes (Chong et al., 2006; Japp and Newby, 2008). Available studies indicate that progression to overt HF resulted in a significant down-regulation of the APJR protein in the myocardium (Dalzell et al., 2015).

While apelin has a cardioprotective effect, AVP stimulates cardiomyocytes remodeling mainly *via* the V1aR (Folino et al., 2015; Chen et al., 2015). The present study showed that the key factor in V1aR mRNA expression in the LV was HF, whereas the V1aR protein level in the LV was significantly higher in the HF HFD rats. We also demonstrated that V1aR mRNA expression in the RV was significantly higher in the SO HFD rats compared with the SO NFD rats. Similarly, the V1aR protein level in the RV was significantly higher in the SO HFD rats. There is still a lack of data indicating the effect of V1aR on morphology and activity of the RV. However, some studies have shown that V1aR mRNA expression in rat cardiomyocytes increased 14 weeks after myocardial infarction (Yamazaki et al., 2012). Other researchers have found that V1aR expression was reduced in rat cardiomyocytes four weeks after myocardial infarction (Chandrashekhar et al., 2003). Murasawa et al. (1995) indicated that among the factors that influence the increase in V1aR gene expression in smooth muscle cells are glucocorticoids, which increase the stability of mRNA. It was proved that patients with HF had an increase in the synthesis and release of glucocorticoids into the circulatory system, such as cortisol (Oakley and Cidlowski, 2015).

Little is still known about the expression and role of V1bR in the heart. Only a few studies describe the prevalence of the V1bR in the myocardium (Lolait et al., 1995; Sellke et al., 2019). In our study, V1bR mRNA expression in the RV was significantly higher in the HF HFD rats. While the V1bR protein level in the RV was higher in the SO NFD rats compared with the SO HFD rats and the HF NFD rats. Additionally, the combination of HF and a HFD resulted in an increase in the V1bR protein level in the RV as well as in the LV. It appears that AVP stimulates the fibrosis process and the remodeling of the myocardium due to the activation of cardiac fibroblasts (Niu et al., 2014). It can be assumed that the above impact of AVP will be affected not only *via* V1aR but also *via* V1bR.

In the current study rats were fed either NFD or HFD, thus the effects of two types of diet on the expression of receptors were dichotomic. Further experiments with varied content of fat in the HFD will allow to determine if the observed effects of high fat intake on the expression of vasopressin and apelin receptors are dose-dependent.

5. Conclusion

Our study showed that post-infarct heart failure and a high fat diet cause significant changes in mRNA expression and protein levels of APJR, V1aR and V1bR in the hypothalamus, in the left and the right ventricles and in the retroperitoneal adipose tissue. Additionally, we have demonstrated that the combination of HF and HFD caused a different effect than either factor separately. The observed changes in the expression of the examined receptors may have important implications for the regulation of cardiovascular function and metabolism. We suppose that the presented results will be helpful in the development of new pharmacological agents in the treatment of cardiovascular diseases in obese people.

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Declaration of Competing Interests

None declared.

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