HOW DOES THE ADMINISTRATION OF VENLAFAXINE AFFECT THE HEART IN THE EXPERIMENTAL MODEL OF METABOLIC SYNDROME?

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Metabolic syndrome, characterized by various symptoms (dyslipidemia, hyperglycemia, obesity, hypertension), could be already called „a modern epidemy “, as it affects more than a quarter of the world human population. Patients with metabolic syndrome are at a higher risk for the development of not only cardiovascular diseases, but also psychiatric disorders, e.g. depression and psychoses. Many studies have found a bidirectional relationship between metabolic syndrome and depression, but the pathomechanisms are still not fully understood. Moreover, depressive patients need to be treated with antidepressants, that could, in turn, lead to worsening or even development of metabolic syndrome or cardiovascular complications. Venlafaxine belongs to the group of dual antidepressants, as it inhibits serotonin, norepinephrine and in high doses even dopamine reuptake. Venlafaxine has been reported to be responsible for cardiovascular adverse effects, such as the development of the hypertensive crisis, but the cardiometabolic risk in venlafaxine treated patients with metabolic syndrome is not explored. This study was focused on the effect of venlafaxine (VE; 10mg/kg BW/day p.o., 3 weeks) administered to hereditary hypertriacylglycerolemic rats fed with high-fat-fructose diet (HFFD; 1% cholesterol, 7.5% lard, 10% fructose) on the parameters determining the presence of metabolic syndrome (lipid profile, glucose tolerance, waist circumference, blood pressure), as well as on the heart. Cardiac electrical function was monitored by recording of the standard ECG in *„in vivo“*conditions and *„ex vivo“* on the isolated spontaneously beating heart perfused according to the Langendorff. Rats were fed with HFFD either for 8 weeks (HFFD 8, n=10; HFFD 8+VE, n=9) or 5 weeks and then it was switched to the standard diet (HFFD 5+3, n=10; HFFD 5+3+VE, n=9). Wistar rats fed with standard diet (n=5) were used as a control group. Changes in biochemical parameters, waist circumference, and blood pressure confirmed the experimental induction of animal metabolic syndrome. However, majority of the observed changes were reversible close to basic levels by the switch of the diet to the standard one. Administration of venlafaxine for the last 3 weeks to rats fed with HFFD for 8 weeks, led to potentiation of the effect of diet on biochemical parameters and further disrupted lipid profile by decreasing serum levels of HDL cholesterol and increasing LDL cholesterol, as well as it increased the blood pressure. After the switch to the standard diet, venlafaxine did not worsen the manifestation of metabolic syndrome and showed tendency to restore the control values. Eight weeks of HFFD caused shortening of PQ interval and prolongation of QRS complex

and QTc interval, and these effects were potentiated by venlafaxine, independently from the diet. Unlike other parameters, values of QTc interval duration were not reversed by the switch of the diet either in presence or absence of venlafaxine, what may increase the risk for the development of dysrhythmias. HFFD showed potential to decrease the value of proarrhythmogenic threshold for the development of sustained ventricular tachycardia or fibrillation after electrical stimulation and prolong the time needed to the restoration of sinus rhythm. Venlafaxine administration in combination with HFFD led to higher susceptibility of the hearts to the life-threatening arrhythmias, but this effect was diminished after the switch to the standard diet. Hearts isolated from HFFD 8 rats had significantly lower left ventricular systolic pressure and slowed rate of contraction and rate of relaxation. Venlafaxine aggravated these changes, together with the increase in heart rate and coronary flow. On the other hand, myocardial changes caused by HFFD seem to be partly reversible by the switch to the standard diet. According to our results, we could conclude that treatment with venlafaxine in individuals suffering from metabolic syndrome represent an additional cardiometabolic risk factor, however, change of a lifestyle by avoiding excessive fat and fructose intake may be a protective measure for the majority of the parameters, even during the treatment with venlafaxine.