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Guest Editor:
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P121-T | Immunohistological detection of FBN1 expression in mouse aorta

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Marfan syndrome (MFS) is a systemic hereditary autosomal dominant disease characterized by connective tissue disorders. Acute aortic syndrome (AAS) including aortic dissection is the cause of death in over 90% of untreated patients. Fibrillin 1 (FBN1) has been identified as the major causing gene of MFS, as nearly 3000 FBN1 mutations has been associated with Marfan disease, but rarely with dissection events. FBN1 is an important structural protein which regulates microfibril stability and assembly. FBN1 mutations disrupt microfibril formation, and eventually weaken the connective tissue. Therefore, dysregulation in FBN1 content could play an important role in aneurysm formation. Histopathology of aneurism is characterized by an enlargement and weakened aortic medial layer, with fibrosis and disorganization and fragmentation of the elastic fibers. We have used two different models of Marfan mice to analyze in aorta gene expression changes in Fbn1.

1. A mouse heterozygous for an allele of Fbn1 (Fbn1C1039G/+ ) containing a mutation, frequently found in MFS patients.

Our results indicate that lentivirus encoding Fbn1 specific shRNA efficiently downregulated aortic Fbn1, leading aortic dilation and medial degeneration. Given the difficulties to detect Fbn1 expression in mouse aortic extracts by Western Blot, we have set up an immunohistological protocol to detect Fbn1 based on digestion of the aortic tissue with elastase. This approach has allowed us to monitor the levels of Fbn1 protein expression in wild type, in Fbn1-deficient mice, and compare them Fbn1 expression in Marfan patients.

P122-T | The influence of methoxamine on the isolated heart chronotropy and inotropy

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It had earlier been shown that the combined blockade of β1-, β2-, and α1-ARs is more effective than the selective blockade of β-ARs, which is widely used in the treatment of cardiac pathologies. α1-AR of the heart participates in numerous physiologic processes, such as inotropy, genes transcription, protein synthesis, glucose metabolism and inhibition of apoptosis. These findings attest to the need of further studies to develop novel approaches in the treatment of cardiac pathologies.

The experiments were carried out on albino rats aged 20 weeks. The rats were anesthetized intraperitoneally with 25% urethane (800 mg/kg body weight). The heart was perfused in a Langendorff System (ADInstruments) with carbogen-oxygenated Krebs–Henseleit solution ex vivo. The retrograde perfusion was driven by constant hydrostatic pressure of 60–65 mmHg. To stimulate α1-ARs, methoxamine (MX, an agonist affecting all subtypes of α1-ARs, Sigma) was used at the concentrations of 10^-10-10^-8 M. The signals were recorded in a PowerLab 8/35 system (ADInstruments) with the help of LabChart Pro 8.0 software. The data was processed statistically using Microsoft Excel software and Student’s t test.

The stimulation of α1-ARs with MX led to bradycardia in the isolated heart. It was also observed that all studied concentrations of methoxamine induced a negative inotropic reaction of the isolated left ventricle of rats. The intensity of the negative inotropic effect depended on concentration of the agonist. Decreased heart rate and myocardium contractility with the activation of α1-AR may be secondary to decreased ICa via the activation of protein kinase C. It is quite possible that α1-AR participates in more delicate regulations of cardiac function and it is most likely that the effects of this stimulation depends on activities of other receptors and different intracellular systems.

Work supported by Program of Competitive Growth of KFU and Russian Foundation for Basic Research.

P123-T | The influence of If inhibition on the myocardium electrical activity

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"Funny currents" (If) play a decisive role in the creation of automatic activities in the cells of mammalian pacemakers. Recently, new data were obtained indicating a possible involvement of If in the performance of working cardiomyocytes. This work was designed to study changes in the shape of the action potential (AP) of rat atrial cardiomyocytes induced by a specific inhibition of If with 10^-5 M
of ZD7288 (an organic blocker) stimulated electrically and also in the absence of this stimulation.

The experiments, which involved the intracellular recording of electrical activities in the working myocardium, were carried out on random-bred albino rats. Isolated right atrial wall from a fragment of the right auricle exhibiting no pacemaker activity was placed in a 3-mL chamber and superfused with Tyrode solution at 38°C at a rate of 10 mL/min. The stimulus duration (1 ms) and repetition rate (5 Hz) corresponded to the normal HR of mature rats. Intracellular AP was recorded via glass microelectrodes with resistance of 25–60 MΩ. The signals were digitized with an E14-140 converter (L-Card) and recorded using PowerGraph 3.3 software (DiSoft). The data were processed with Mini-Analysis 3.0.1 software (Synaptosoft), Microsoft Excel software and Student’s t test.

ZD7288 significantly increased the duration of action potentials at 50% and 90% repolarization levels in atrial myocardium at a fixed stimulation rate of 5 Hz. The blocker affected neither resting nor the upstroke velocity of action potential.

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P124-T  The blockade of If in isolated (Langendorff perfused) heart

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According to modern views, If are responsible for the development of initial, linear, and slow diastolic depolarization in cells of the sinoatrial node. At the same time, a rather small If was identified in both atypical and working cardiomyocytes. Therefore, it remains unclear how the blockade of data currents affects heart function.

This research aim is to investigate dose-dependent effects of the blockade of If: on coronary flow; on the inotropy; and the chronotropy in Langendorff perfused heart in adult rats. Isolated hearts were perfused in a Krebs-Henseleit solution – Langendorff (ADInstruments) installation. The coronary flow (CF), systolic pressure in the left ventricle (LVP) and heart rate (HR) were calculated along the curve. The signals were recorded in a PowerLab system (ADInstruments) with the help of LabChart Pro 8.0 software. 10−9–3 × 10−5 M concentrations range of ZD7288 (Sigma) were used for the blockade of If. The data was processed statistically using Microsoft Excel software and Student’s t test.

ZD7288 10−9 M increased LVP by 47% (P ≤ 0.05), decreased HR by 26% (P ≤ 0.05) and reduced CF by 20% (P ≤ 0.01). ZD7288 10−8 M, 10−7 M and 10−5 M did not cause significant alterations in the studied parameters of the heart. ZD7288 10−6 M led to bradycardia – 23% (P ≤ 0.05) and did not cause significant changes in LVP and CF. ZD7288 3 × 10−6 M reduced LVP by 14% (P ≤ 0.05), HR by 11% (P ≤ 0.05) and did not lead to a change in CF. If blockade 3 × 10−5 M reduced myocardial inotropy by 26% (P ≤ 0.05), CF by 14% (P ≤ 0.01) and HR by 19% (P ≤ 0.05).

The blockade of If in Langendorff perfused hearts of adult rats resulted in different contractility effects. The range in all the studied concentrations of the If blockade reduced both heart function and coronary flow.

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P125-T  Role of NPY1,5-receptors in the neonatal rats myocardial contractility

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Neuropeptide Y (NPY) is present in the central and peripheral nervous systems and fully satisfies to neurotransmitter criteria, since it is stored in sympathetic vesicles, released by electrical stimulation and acts on specific receptors. In the rat heart there are metabolotropic Y1R, Y2R, Y3R, Y4R and Y5R receptors. The density of different receptor subtypes varies in postnatal ontogenesis. Expression of Y1R increased between 10 and 20 days of life. A small number of Y2R is observed in the atria and ventricles only from 20 days of life. In contrast, the highest level of expression of Y5R was found in newborn pups comparing with more adult rats.

The aim of the current study was to determine the role of different subtypes of NPY receptors in the heart contraction in the postnatal development. Registration of isometric contraction of atrial and ventricular myocardial striae of 7- and 100-day-old rats was carried out on a PowerLab device with a force sensor MLT 050/D (ADInstruments). The selective agonist of Y1R, Leu(31)Pro(34)NPY (10−5–10−13 M), induced an increase in myocardial contraction force in 7-day-old (10−6 M) and in 100-day-old rats (10−7 M). The selective blocker of Y1R, BIBP 3226,