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Exercise does not prevent cardiac autonomic dysfunction in rats treated with anabolic steroids

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The aim of this study was to evaluate the changes in HRV induced by administration of nandrolone decanoate (ND), with or without exercise during 8 weeks (W). 40 male rats were divided into four groups: sedentary (DS) and trained (DT) treated with ND; sedentary (CS) and trained (CT) treated with vehicle. Exercised were carried 5 days/W. ECG was recorded at 0, 4th and 8thW. Time- and frequency-domain analysis of heart rate variability was performed. SDNN and RMSSD were reduced in DT (7.81 ± 2.85 ms) and DS (6.21 ± 1.13 ms) compared to CS (9.6 ± 2.6 ms) after 4th and 8thW (DT: 7.02 ± 3.17 ms, DS: 4.6 ± 1.12 ms vs CS: 8.4 ± 1.1 ms); pNN5 was reduced only after 8thW (DT: 23.3 ± 5.7 ms, DS: 14.3 ± 6.3 ms vs CS: 33.2 ± 8.5 ms). CT showed increase in RMSSD and pNN5% after 8W, compared to CS (RMSSD = 10.47 ± 2.36 ms vs 8.38 ± 1.1 ms; pNN5% = 43.2 ± 9 vs 33.2 ± 8.5). High frequency (HF) of DS and DT was reduced compared to CS after 4th (6.65 ± 6 ms², 4.9 ± 1.7 ms² vs 12.8 ± 2.63 ms²) and 8th (5.34 ± 3.39 ms², 4.16 ± 0.93 ms² vs 11.54 ± 1.6 ms²) while LF/HF ratio increased after 4th (2.1 ± 1.3 , 1.95 ± 0.83 vs 0.9 ± 0.2) and 8th (2.08 ± 1.0 , 2.5 ± 0.44 , 0.85 ± 0.14). CT had a rise in HF compared to CS on 8thW (14.75 ± 2.44 ms² vs 11.5 ± 1.6 ms²). A Supraphysiological dose of ND induces cardiac autonomic dysfunction and regular exercise does not prevent this effects.

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Mg²⁺-inhibitable TRPM7-like cation current in human atrial myocytes

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The aim of our work was to identify the presence of TRPM7-like current in human atrial myocytes, and to investigate the potential role of these channels in the electrical activity of atrial cells during atrial fibrillation (AF). Myocytes were isolated from right atria biopsies from 72 adult patients in sinus rhythm (SR) and 49 patients in AF. We demonstrate that in both patient groups under voltage clamp, with voltage-dependent and other ion channels inhibited, cells dialyzed with low intracellular free [Mg²⁺]_i produced outward-rectifying TRPM7 currents that could be suppressed by raising extracellular [Mg²⁺]_o or by application of Gd³⁺ and 2-APB (at 100 μM), known to block TRP channels. The current was absent in cells dialyzed with physiological free [Mg²⁺]_i or MgATP, but that did not protected from the spontaneous run-up in divalent free external solutions. In addition, we established that

the density of activated TRPM7-like current in cells from patients with AF was higher as compare with those with SR (5.30 ± 0.39 and 3.62 ± 0.23 pA/pF, respectively, at +80 mV, $p < 0.001$). In conclusion: this is the first study, which describes TRPM7-like current in native human atrial cardiomyocytes that operates under pathophysiological conditions.

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Clustering of voltage-gated sodium channel Na_v1.8 in lipid rafts is essential for action potential propagation in nociceptive unmyelinated axons

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It has been over 15 years since sensory neuron-specific sodium channel Na_v1.8 was identified. Since then Na_v1.8 has been shown to play a crucial role in pain pathways, and it became a prominent drug target for novel pain killers. In contrast to myelinated neurons, mechanisms that target voltage-gated sodium channels to the unmyelinated C-fibre axons are largely unknown. We investigated the localisation of Na_v1.8 in unmyelinated primary sensory neurons. Na_v1.8 was found to be clustered in lipid rafts on unmyelinated axons. When the lipid rafts are disrupted, remarkable reduction in both the conduction velocity and the number of cells responsive to mechanical stimuli to the unmyelinated axons were seen. Using a compartment culture system, we also found that disruption of rafts in the middle region of the sensory axons caused a significant reduction in the responsiveness of the neurons to chemical stimuli to nerve endings. This is due to the failure of action potential propagation through the axons. These data suggest that clustering of Na_v1.8 in lipid rafts of unmyelinated fibres is a key factor for the functional properties of the channel, which may be due to a change in the voltage threshold. Disruption of the Na_v1.8 cluster and modifying lipid rafts in primary sensory neurons may be a useful new approach to control the excitability of nociceptive neurons.

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Effect of ion channel blockers on T-lymphocytes stimulated with anti-CD3 and anti-CD28

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Ion currents in are crucially important for activation of T-lymphocytes. Our aim was to investigate how the blockage of various ion channels in isolation or in combination affects mitogen-dependent activation and proliferation of T-cells. We activated human peripheral blood lymphocytes using monoclonal antibodies against the TCR-CD3 complex and CD28. We applied specific channel blockers inhibiting the major ion channels of the T-cell: either the Kv1.3 (TEA or Anurotoxin), IKCa1 (TRAM-34), or the CRAC channel (2-APB) alone or in combination. Five days after the stimulus we measured the change in cell size and cellular granulation with

flow cytometry along with the proportion of dividing cells, using CFSE (carboxyfluorescein succinimidyl ester) dilution assay. Our measurements indicated that the ion channel blockers suppressed the proportion of dividing cells in a dose-dependent manner. Increasing the strength of the stimulation reduced the potency of the blockers to inhibit cell proliferation and eventually the blockers were ineffective in decreasing lymphocyte proliferation. We experienced the greatest amount of inhibition using the combination of the blockers, which indicates synergy in the regulation pathway of the various ion channels.

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Quantitative NaPi2b transporter expression in different histomorphological types of ovarian cancer

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Recently, sodium dependent phosphate transporter NaPi2b was revealed as potential marker for breast, thyroid and ovarian cancer. In vivo, NaPi2b is involved in maintenance of phosphate homeostasis and mutations or aberrant expressions of its gene (SLC34A2) are associated with several diseases including cancer. However, data about NaPi2b mRNA expression in different types of cancer and correspondent normal tissues are controversial and restricted. We investigated SLC34A2 gene expression level in normal ovarian tissues and different histomorphological types of ovarian tumors using real-time PCR analysis. It was found that SLC34A2 gene was highly expressed in well-differentiated endometrioid and papillary serous tumors, but was not expressed in low-differentiated tumors, benign tumors and in most normal tissues. mRNA expression of SLC34A2 in serous and endometrioid ovarian tumors accurately correlated with protein expression that was detected in these tumor samples by Western blot analysis and immunohistochemistry in our previous investigation. Upregulation of SLC34A2 gene expression in well-differentiated tumors may reflect cell differentiation processes during ovarian cancerogenesis and could serve as potential marker for ovarian cancer diagnosis and prognosis.

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Membrane-permeant inhibitors of the potassium channel Kv1.3 induce apoptosis in cancer cell lines

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Potassium channels are emerging therapeutic targets in cancer. Kv1.3 has been shown to play an important regulatory role during proliferation and apoptosis. In lymphocytes and other cells Kv1.3 is present in both the plasmamembrane and the inner mitochondrial membrane (mitoKv1.3). Inhibition

of mitoKv1.3 by pro-apoptotic Bax results in production of reactive oxygen species and leads to cytochrome c release and death. Three distinct membrane-permeant inhibitors of Kv1.3 induce apoptosis in different cancer cell lines expressing mitoKv1.3, while membrane-impermeant inhibitors do not induce cell death, suggesting that apoptosis involves inhibition of mitochondrial and not of plasma membrane Kv1.3. The effect of these drugs is abolished when Kv1.3 is absent or its expression is reduced by siRNA, demonstrating Kv1.3-specificity of the inhibitors. Most importantly, the drugs are able to induce death in two cell lines lacking Bax and Bak. Our work thus identifies a novel pharmacological tool to induce apoptosis in mitoKv1.3-expressing cells and in vivo experiments are under way to test sensibility of tumors to these drugs.

New and notable

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Protein Dynamical Transition and Resolution Effects on Mean Square Displacement in Lysozyme Systems

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In the present contribution a procedure for molecular motion characterization based on the evaluation of the Mean Square Displacement (MSD), through the Self-Distribution Function (SDF), is presented. It is shown how MSD, which represents an important observable for the characterization of dynamical properties, can be decomposed into different partial contributions associated to system dynamical processes within a specific spatial scale. It is shown how the SDF procedure allows us to evaluate both total MSD and partial MSDs through total and partial SDFs. As a result, total MSD is the weighed sum of partial MSDs in which the weights are obtained by the fitting procedure of measured Elastic Incoherent Neutron Scattering (EINS) intensity. We apply SDF procedure to data collected, by IN13, IN10 and IN4 spectrometers (Institute Laue Langevin), on aqueous mixtures of two homologous disaccharides (sucrose and trehalose) and on dry and hydrated (H₂O and D₂O) lysozyme with and without disaccharides. The nature of the dynamical transition is highlighted and it is shown that it occurs when the system relaxation time becomes shorter than the instrumental energy time. Finally, the bioprotectants effect on protein dynamics and the amplitude of vibrations in lysozyme are presented.

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DNA damage in breast cancer cells treated with combination of quercetin and anticancer drugs

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Quercetin (Q) is a natural flavonol present at high levels in numerous of plants. It has been epidemiologically associated with bioactive protective effects, but has also been shown to be mutagenic and toxic in *in vitro* cell systems.

Absztraktfordítás:

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Ioncsatornablokkolók hatása az anti-CD3-mal és anti-CD28-al stimulált T-limfocitákon

A T-sejtek ioncsatornáinak nagy szerepe van ezen sejtek aktivációjában. A célunk az volt, megbemutassuk a különböző ioncsatornablokkolók hatásait, mind külön-külön vagy kombinációban, a mitogénnel kezelt limfociták aktivációjára és proliferációjára.

A humán perifériás vérből származó limfocitákat a TCR-CD3 komplex elleni aktiváló típusú antitestekkel, anti-CD3-mal és anti-CD28-cal aktiváltuk. Ezt követően a sejteket kezeltük különféle ioncsatornagátlókkal, melyek a T-sejt főbb ioncsatornáinak ellen hatnak: a Kv1.3 csatorna gátlására TEA-t és Anuroctoxint, az IKCa1 gátlására TRAM_34-et, továbbá a CRAC csatorna blokkolására 2-ApB-t alkalmaztunk. Öt nappal a stimulust követően megmértük a sejtméretet és granuláltságot áramlási citometria segítségével, majd az osztódó sejtek arányát vizsgáltuk CFSE-hígítási esszé használatával.

Eredményeink megmutatták, hogy az ioncsatornagátlók dóziszfüggően képesek a sejtosztódást gátolni. Amennyiben viszont emg növeltük a stimuláció mértékét, azt figyelhattuk meg, hogy a sejtosztódásra gyakorolt gátló hatása a gátlószereknek egyre csökkent, majd kioltódott. A legnagyobb mrétékű gátlást akkor tapasztaltuk, amikor a gátlószereket kombinációban alkalmaztuk, ami egy szinergisztikus hatást jelenthet.