

Experimental models of kidney diseases to study pathogenetic mechanisms and efficacy of pharmacological correction against the background of comorbid pathology

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The aim of our study is to report about modern models of kidney diseases associated with other pathological conditions for experimental studies of pathogenetic mechanisms and efficacy of pharmacological correction.

The study deals with experimental models reasonably to be applied in investigation of comorbid pathology pathogenesis and efficacy of its pharmacological correction. The attention is focused on the models of cardio-renal, hepatic-renal syndromes and multiple organ hypoxic histochemical injury simulated in laboratory rats. These models are characterized by easy modeling, simulation of comorbidity pathogenesis, acute and chronic periods of diseases available, induced by the antibiotic Doxorubicin or exotoxins – corrosive sublimate, sodium nitrite, and 2,4-dinitrophenol.

Conclusions. The models of cardio-renal, hepatic-renal syndromes and hypoxic histochemical injury of the body are found to be optimal to perform multipurpose studies of physiological, pathophysiological, pharmacological directions with maximal similarity of the results obtained to clinical-therapeutic peculiarities of comorbid pathology.

Експериментальні моделі захворювань нирок для досліджень патогенетичних механізмів та ефективності фармакологічної корекції на тлі коморбідної патології

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Мета роботи – висвітлення сучасних моделей захворювань нирок, що поєднані з іншими патологічними станами, для експериментальних досліджень патогенетичних механізмів та ефективності фармакологічної корекції.

Розглянуті експериментальні моделі, які доцільно використовувати для дослідження патогенезу та ефективності засобів фармакологічної корекції коморбідної патології. Акцентовано увагу на моделях відтворення кардіоренального, гепаторенального синдромів і поліорганного гіпоксичного гістогемічного пошкодження у лабораторних щурів. Цим моделям властиві легке моделювання, відтворення патогенезу коморбідних захворювань, наявність гострого та хронічного періоду пошкодження, індукованого антибіотиком доксорубіцином чи екотоксикантами – сулемою, нітритом натрію, 2,4-динітрофенолом.

Висновки. Описані моделі кардіоренального, гепаторенального синдромів і гіпоксичного гістогемічного пошкодження організму є оптимальними для здійснення багатоцільових досліджень фізіологічного, патофізіологічного, фармакологічного спрямування з максимальним наближенням результатів до клініко-терапевтичних особливостей коморбідної патології.

Экспериментальные модели заболеваний почек для исследований патогенетических механизмов и эффективности фармакологической коррекции на фоне коморбидной патологии

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Цель работы – освещение современных моделей заболеваний почек, сочетанных с другими патологическими состояниями, для экспериментальных исследований патогенетических механизмов и эффективности фармакологической коррекции.

Рассмотрены экспериментальные модели, которые целесообразно использовать для исследования патогенеза и эффективности средств фармакологической коррекции коморбидной патологии. Акцентировано внимание на моделях, воспроизводящих кардиоренальный, гепаторенальный синдром и полиорганное гипоксическое гистогемическое повреждение у лабораторных крыс. Эти модели характеризуются легким моделированием, воспроизведением патогенеза коморбидных заболеваний, наличием острого и хронического периода повреждения, индуцированного антибиотиком доксорубицином или экотоксикантами – сулемой, нитритом натрия, 2,4-динитрофенолом.

Выводы. Представленные модели кардиоренального, гепаторенального синдромов и гипоксического повреждения органа являются оптимальными для проведения многоцелевых исследований физиологического, патофизиологического, фармакологического направлений с максимальным приближением результатов к клинико-терапевтическим особенностям коморбидной патологии.

Modern conception concerning disease, first of all, assumes understanding of specific symptoms peculiar for pathological processes, their functional and biochemical markers. Although the whole set of separate signs of disease is a considerable real content of clinical manifestation, it does not enable to assess adequately a patient's organism on the whole. The fundamental component based on the general theoretical ideas concerning the essence of disease is rather important for cognition. It refers to the initial cause of interaction with the body and regular further development of new, regardless of an etiology, pathological changes on the level of organs and systems [1]. According to the principles of integrative body response, physiological compensatory mechanisms from the side of undamaged organs are the bases for pathophysiological interrelations and simultaneous formation of several diseases. Therefore, nowadays comorbid diseases and comorbid pathology in the majority of cases are considered not as accidental combination of pathological processes, but rather as their determined combination [2].

The conception concerning interdependent and interactive diseases determines a modern strategy of preventive measures and treatment of comorbid pathology. First of all, it is administration of pharmaceutical agents with universal mechanisms of multiple organ protective effects. Considerable success in medicine connected with improvement of diagnostic methods and introduction of newest therapeutic technologies have not completely solved the problem of comorbidity. Comorbid pathology makes the period of treatment substantially longer, increases the risk of severe stages development, and remains the situation requiring reasonable combined therapy and search for new methods of pathogenetic treatment [3–5].

It should be noted that clinical assessment of potential and existing pharmacological correctors of multiple organ dysfunction is preceded by the stage of careful pre-clinical trials. Development of an experimental model with combination of signs corresponding to the pathological processes similar to those of human organism is rather complicated task. In spite of numerous existing and well-approved methods, the process of development and improvement of the methods to simulate diseases of the organs and systems is continuous. Special difficulties are associated with the choice of a model reflecting several pathological processes – common in their etiology and mechanisms of activation and progress. At the same time, adequate experimental model to a certain clinical situation enables to expand the knowledge concerning pathogenesis of comorbidity, elaborate new directions in the treatment of comorbid pathology and assess objectively the possibility of extrapolation of the experimental study results into clinical practical work.

The aim

The aim of our study is to report about modern models of kidney diseases associated with other pathological conditions for experimental studies of pathogenic mechanisms and efficacy of pharmacological correction.

It should be noted that the models of kidney pathology as a constituent of experimental comorbidity are of special interest. Kidneys have certain priority in functional-metabolic

supply of the vital organs – the brain, heart, lungs, and liver [6–9]. Thus, modern directions of cardiac therapy are focused on early detection and optimal correction of pathological interdependent effects, which first of all are associated with kidneys [10–13]. Pathophysiological relations between the heart and kidneys, associated by common mechanisms, so-called cardio-renal syndrome (CRS), remain in the center of attention of experimental and clinical workers.

One of the generally known methods to simulate myocardial injury and functional disorders of the cardio-vascular system is administration of anti-tumour antibiotic of anthracycline group – Doxorubicin (DXR) [14–16]. Doxorubicin-simulated cardiomyopathy as a model was used in our study to investigate the efficacy of new cardio-vascular agents – calcium channel blockers of dihydropyridine group and potassium channel activators of the guanidine group [17]. The experiments were conducted on nonlinear mature rats of both sexes by means of slow intraperitoneal DXR injection at a dose of 5 mg/kg per body weight weekly for four weeks. Clinical administration of DXR is an important fact to induce not only cardio-, but also nephro- and hepatotoxicity [18–20]. Therefore, interpretation of results assumes effect of the examined compounds on other toxic targets of the applied DXR dose as on the constituents of comorbidity.

In our study we concentrated our attention on investigation of the efficacy of generally known kidney protectors – renin-angiotensin system blockers as well as melatonin in case of nephropathy induced by a single intravenous DXR injection in the dose of 5 mg/kg in Wistar rats [21]. The period of observation in both experimental studies was 28 days – the time necessary for the models of cardio- and nephropathy formation, which is indicative of possible DXR use in the dose of 5 mg/kg for pathophysiological analysis and improvement of cardio-renal pathology treatment.

In addition to prevention of DNA and RNA synthesis, DXR is known to induce the formation of highly toxic free radicals of oxygen that cause necrotic-dystrophic disorders in the liver cells. At the same time, mitochondria-rich hepatocytes (about 1000 per 1 cell) are damaged, energy deficiency, pathological changes of biochemical indices and structural-functional liver organization occur [22,23]. Liver damage caused by DXR injection to rats in the total dose of 20 mg/kg according to the methods [17], proved the results of glucosamine derivatives investigation as possible correctors of hepatotoxic action produced by the anthracycline antibiotics [24]. It should be noted that hepato- and cardio-protective action of taurine zinc solid dispersions was assessed in Sprague-Dawley rats after intraperitoneal injection of DXR in the dose of 3 mg/kg (7 injections, the total dose 21 mg/kg) during four weeks [25]. Thus, on the 28th day of DXR administration in the total dose of 20–21 mg/kg Doxorubicin-induced cardiomyopathy is associated with kidney and liver damage.

It should be noted that renal and hepatic dysfunctions are pathogenic bases of hepatorenal syndrome (HRS). Hepato- and nephrotoxicity of many pharmacological agents, environmental heavy metal pollution and other exotoxins create a role for studies directed to specification of diagnosis and detection of effective means to prevent the development of HRS. Corrosive sublimate nephropathy is a classical model with prevailed proximal nephron

damage – a universal link in the mechanism of nephric pathology [26–28]. Disorders of the kidney functional state in nonlinear albino rats after a single subcutaneous injection of 0.1 % mercury dichloride solution is manifested on the very first day of nephropathy modeling [29]. Similar injection of corrosive sublimate in the dose of 5 mg/kg induces biochemical, degenerative and necrotic changes in the liver and kidneys of rats manifested 24 hours after simulation of acute mercury intoxication, and are corrected by Silymarin [30]. Mercury derivatives belong to the most dangerous (and usually extremely toxic) chemical substances, and hepatotoxicity occurs when a wide range of doses and very low levels are administered [31]. The model of sublimate nephropathy in rats, induced by the dose of 5 mg/kg, is considered as an adequate to study the combined injury of liver and kidney due to the thoroughly studied pathogenesis of HRS using this model [32]. An early period of a polyuric stage of sublimate-induced nephropathy in rats (72 hours after subcutaneous injection of mercury dichloride in the dose of 5 mg/kg) is known to be characterized by biochemical and morphofunctional signs indicative of the tubular portion of nephron and functional zone III of the liver lobule damage and HRS formation [32].

Experimental models of multiple organ hypoxic injuries are reasonable to be used in order to specify new mechanisms and improve pathogenetic therapy of comorbid conditions. Bioenergetics mechanisms of hypoxia pathogenesis are the bases of non-specific pathologic processes formed on the systemic level in response to oxygen deficiency in the body. Moreover, damage to organs worsens their hypoxia and, in its turn, hypoxia increases the progress of diseases and vice-versa [33–35]. The search for pharmacological agents for simultaneous correction of a limiting injury and energy-dependent processes of the vital organs most susceptible to hypoxia is of great practical value. There is no doubt that administration of pro-hypoxic factors in experimental animals or pathogenic changes of oxygen partial pressure in the inhaled air modeling lead to polyfunctional consequences of oxygen deficiency. At the same time, natural activation of adaptive-compensatory reactions with reduced intracellular ATP level, even under conditions of repeated hypoxia, makes certain difficulties in the model selection. It mostly refers to the post-hypoxic long-term studies with the aim to examine the effect of treatment agents under conditions of chronic processes development. On the basis of it, we have suggested and tested the method of comorbid hemic and histotoxic hypoxia modeling in nonlinear albino rats. The model was simulated by single subcutaneous injection of sodium nitrite in a dose of 50 mg/kg, and 30 minutes later – 2,4-dinitrophenol in a dose of 3 mg/kg intraperitoneally [36]. Components of pathogenesis in sodium nitrite intoxication are methemoglobin formation and the blood transport function disorders; under the influence of 2,4-dinitrophenol, the processes of oxidation and phosphorylation are broken down in mitochondria, and primary hypoxia of tissues occurs [37]. Both toxins are actively used to model the hypoxic nephropathy including HRS [38–40].

Combination of both hypoxic factors in our studies resulted in the development of acute hypoxic histohemic nephropathy with tubular dysfunction on the day of modeling. On the 30th day, changes of the morphofunctional

kidney state were indicative of the chronic process formation. A sufficiently long period of post-hypoxic disorders allowed investigating nephroprotective effects of Flocalin and Diltiazem, potassium and calcium channel modulators under conditions of acute and chronic hypoxic damage to the kidneys [41,42]. It should be noted that a low level of oxygen in tissues is a peculiar feature of a wide spectrum of organs and systems diseases including those of oncological and infectious pathology. Meanwhile, environmental pollution provides increased conditions for hypoxia. Therefore, the model simulated in our study is reasonable to be used in further investigations concerning pathogenesis of comorbid effect of two powerful exotoxins on the target organs and assessment of therapeutic efficacy to correct multiple organ dysfunction in case of histohemic hypoxia.

Conclusions

Therefore, the above models deserve consideration while choosing the methods of experimental injury of several vital organs. The advantages of these models are simple and correct modeling, reconstruction of common pathogenic links of comorbid pathology, rapid development of acute injury, opportunity to study during the chronic stage of pathological processes, and economic reasonability. At the same time, inductors of the suggested models are the therapeutic agent of a wide spectrum for neoplastic diseases – antibiotic Doxorubicin, existing exotoxins: corrosive sublimate, sodium nitrite, 2,4-dinitrophenol, which is of certain practical value. Therefore, suggested models may be considered as optimal to use in the multipurpose physiological, pathophysiological and pharmacological studies, as their results reflect the clinical and therapeutical peculiarities of comorbid pathology to the maximum extent.

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