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Unexpected effects of old drugs – antihypoxic properties of lactulose

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«Can you teach old drugs new tricks?» Nicola Nosengo asked in 2016 [1]. Faced with skyrocketing costs for developing new drugs, researchers are looking at ways to repurpose older ones – and even some that failed in initial trials. The answer to this question was given back in 1988 when James White Black with Gertrude Elion and George Hitchings were awarded the Nobel Prize in Physiologyand Medicine «For the discovery of important principles of drug therapy». The main conclusion of this work is that «...the most fruitful basis for the discovery of a new drug is to start with an old drug».

The process of finding new uses outside the scope of the original medical indication for existing drugs is also known as redirecting, repurposing, repositioning and reprofiling. For instance, the National Global Cancer Network estimates that 50–75% of drugs in the US are used off-label [2].

Lactulose was first made in 1929, and has been used medically since the 1950s [3]. Lactulose is made from the milk sugar lactose, which is composed of two simple sugars, galactose and glucose [4]. It is on the World Health Organization's List of Essential Medicines. It is available as a generic medication. In 2021, it was the 265th most commonly prescribed medication in the United States, with more than 1 million prescriptions.

Thus, lactulose is a well-known synthetic sugar used to treat constipation. It is broken down in the colon into products that pull water out from the body and into the colon. This water softens stools. Lactulose is also used to reduce the amount of ammonia in the blood of patients with hepatic encephalopathy [5]. It is administered orally for constipation, and either orally or rectally for hepatic encephalopathy. It generally begins working after 8–12 hours, but may take up to 2 days to improve constipation.

Common side effects include abdominal bloating and cramps. A potential exists for electrolyte problems as a result of the diarrhea it produces. No evidence of harm to the fetus has been found when used during pregnancy. It is generally regarded as safe during breast feeding and it is classified as an osmotic laxative [6].

There seem to be no other options for the therapeutic use of lactulose. However, based on a number of theoretical considerations about the possible metabolic and electrical transformations of lactulose and the effects of its derivatives, we decided to test this compound as an antihypoxic agent [7].

The aim of study – to test experimentally the hypothesis about the pos-

sible antihypoxic effect of the drug lactudose *in vitro*.

Materials and methods. All animal studies were performed in accordance with the recommendations of the «European convention for the protection of vertebrate animals used for experimental and other scientific purposes» and approved by the Institutional animal care and use committee. Experiments were performed on 6–8 weeks male Wistar rats (weight 250–300 g) housed under controlled environmental conditions (21 °C, 12 h–12 h light–dark cycle) and free access to water and standard rodent chow.

Experiments in vascular smooth muscles

Adult male Wistar rats (250–275 g) were anesthetised using alpha chloralose, 40 mg/kg, plus urethane, 400 mg/kg b/w, i. p. and then euthanized by cervical dislocation.

The portal vein was chosen as object of the study for the following reasons. Firstly, it has clearly expressed electrical and contractile activity (myogenic automaticity). Secondly, it is a generally accepted model of resistance vessels [8]. And thirdly, in ancient times it played the role of the heart in cyclostome fish – hagfish.

Segments of rat portal vein were cut out, cleaned of both connective and adipose tissue. Then, the portal vein was cut to a longitudinal strip with a width of 1 mm and a length of 3–4 mm. The tissue bath was perfused with a modified Krebs-bicarbonate buffer of the following composition (mM): NaCl, 133; KCl, 4.7; $NaHCO_3$, 10; NaH_2PO_4, 1.38; $CaCl_2$, 2.5; $MgCl_2$, 1.2; HEPES, 10; glucose, 7.8; pH 7.3 at temperature 37 °C. To decrease pO_2 in buffer solution, it was gassed with nitrogen. All preliminary procedures were performed at room temperature in a nominally Ca^{2+} – free physiological salt solution.

Then, vascular strips were mounted isometrically in a tissue bath at a volume of 0.6 ml between a stationary stainless-steel hook and an isometric force transducer (AE 801, SensoNor, A/S, Norten, Norway) coupled to an AD converter Lab-Trax-4/16 (World Precision Instruments, Inc., Sarasota, USA). The tissue bath was equipped with platinum Ag/Cl polarographic electrodes connected with polarographic analyser PA-3 (Laboratorni Pristroje, Praha, Czech Republic) and stimulating platinum electrodes (electronic stimulator SEN-1101, Nihon Cohden, Tokyo, Japan). The vascular strips were lengthened sufficiently to produce a passive force at 4–6 mN. Then the strips were equilibrated for 1 hour at a resting tension. Following the equilibration period, the vascular strips were exposed several times to norepinephrine (NE, 10^{-6} M) or electrical simulation (10 V, 20 msec, 8–16 Hz) until reproducible contractile responses were obtained.

Chemicals and solutions

Lactulose was from the pharmaceutical company «Viola», Zaporpozhye, Ukraine. All other necessary compounds were obtained from Sigma Aldrich (St. Louis, USA).

Results and discussion. The spontaneous activity of the portal vein – as an example of a blood vessel with highly pronounced electrical and mechanical spontaneous activity. It therefore appears permissible to take smooth muscle of portal vein as the functional basis of vascular smooth muscle in general. The typical patterns of portal vein spontaneous contractile activity as well electrically induced increase in contractile force before and under decrease in bath pO_2 (hypoxia) are shown in Figure 1, 2. It should be

noted that lactulose itself at a concentration of 10^{-4} M had no effect on the autorhythmic activity of the portal vein under conditions of normal oxygenation. It is clear that the lowering of the pO_2 in organ bath exerted a pronounced effect on spontaneous and electrically induced smooth muscle (SM) contractile activity. It was shown that the decrease in bath pO_2 from 142–147 mm Hg to 10–8 mm Hg caused gradual and clearly expressed inhibition in myogenic spontaneous contractile activity, and at the bath pO_2 below 12 mm Hg spontaneous activity of the rat portal vein ceased completely. Hypoxia also led to a significant decrease in the level of isometric tension caused by electrical stimulation of smooth muscles.

The effects of hypoxia were completely reversible, i. e. redevelopment of SM contractile activity upon return to normoxia was full and corresponded to prehypoxic level within 5–7 min of reoxygenation.

Surprisingly, lactulose (10^{-4} M) demonstrated a clearly expressed ability to restore spontaneous activity of the rat portal vein inhibited under hypoxia. Figure 1 shows that lactulose, being added to the bath solution against the background of pronounced decrease in spontaneous myogenic activity caused by hypoxia, possess the ability partially restore spontaneous activity of portal vein suppressed under hypoxia.

The next Figure 2 shows typical response of the rat portal vein to field electrical stimulation (ES, 8 Hz, 20 ms, 13 V) at the normal level of organ bath oxygenation (142 mm Hg). The amplitude of this response appears to be greatly decreased under hypoxia, 20 mm Hg (Figure 3).

Thus, if under conditions of normal oxygenation, the amplitude of the plateau isometric tension of smooth muscles

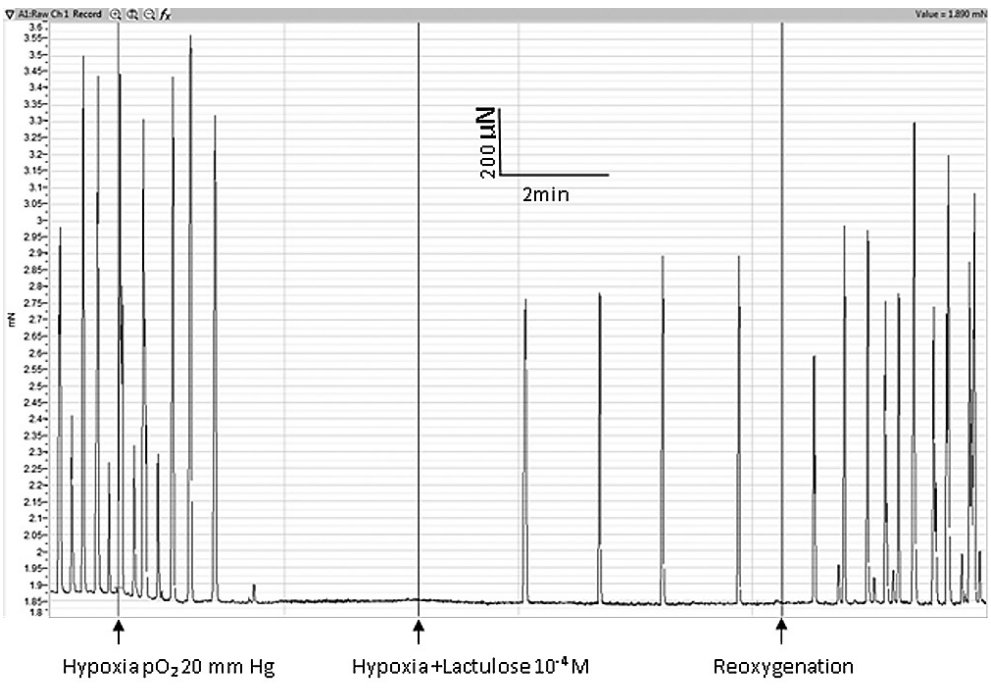

Figure 1. Original contractile recordings the effect of lactulose (10^{-4} M) application on spontaneous activity of rat portal vein suppressed under hypoxia (20 mm Hg) impact

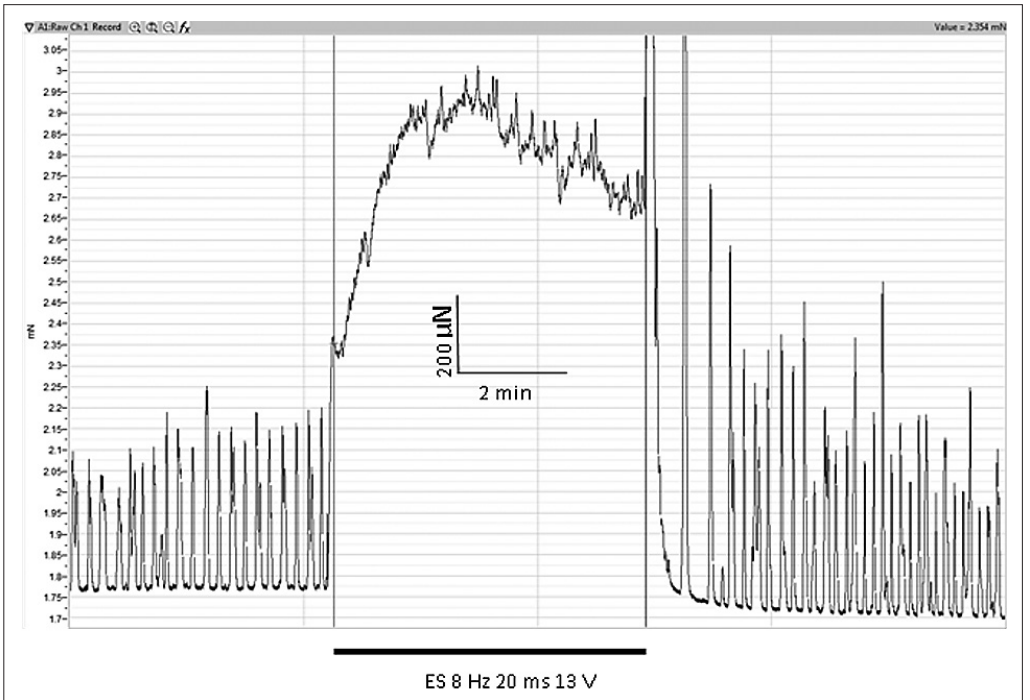

Figure 2. Contractile response of the rat portal vein to field electrical simulation (8 Hz, 20 ms, 13 V) under normal oxygenation (142 mm Hg)

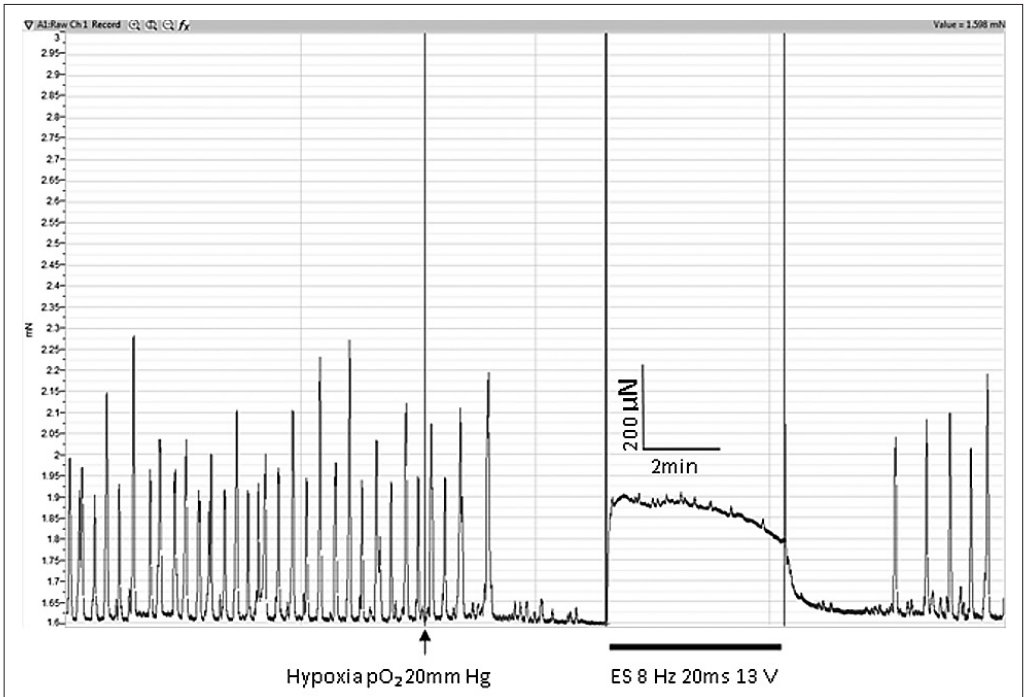

Figure 3. Contractile response of the rat portal vein to field electrical simulation (8 Hz, 20 ms, 13 V) under hypoxia (20 mm Hg)

in response to electrical stimulation averaged (2.9 ± 0.3) mN, then under conditions of hypoxia this value decreased to (1.85 ± 0.1) mN (n = 10, P < 0.05). The addition of lactulose to the perfusate led to an increase of this parameter to (2.1 ± 0.1) mN (n = 12, P < 0.05) (Figure 4).

In case of lactulose was added to the organ bath perfusate before hypoxic impact and electrical stimulation, the stimulation induced paradoxical increment in isometric tension (Figure 5).

All these effects, frankly speaking, is really unexpected and difficult to explain. Let's look at what happens to lactulose when taken orally. Lactulose (4-O-beta-D-galactopyranosyl-D-fructose) is a disaccharide consisting of residues of galactose and fructose molecules, a synthetic structural isomer of milk sugar – lactose, not found in nature. It is generally accepted that lactulose is not absorbed in the small intestine nor broken down by human enzymes, thus stays in the digestive bolus through most of its course, causing retention of water through osmosis leading to softer, easier-to-pass stool. It has a secondary laxative effect in the colon, where it is fermented by the gut flora, producing metabolites which have osmotic powers and peristalsis-stimulating effects (such as acetate), but also methane associated with flatulence.

Lactulose is metabolized in the colon by bacterial flora into short-chain fatty acids, monosaccharides, lactic acid and acetic acid, volative fatty acids, hydrogen and methane. These partially dissociate, acidifying the colonic contents increasing the H^+ concentration in the gut [8]. This favour the formation of the nonabsorbable NH_4 from NH_3, trapping NH_3 in the colon and effectively reducing plasma NH_3 concentrations. Lactulose is therefore effective in treating hepatic encephalopathy as it was indicated before, but specifically, it is effective as secondary prevention of hepatic encephalopathy in people with cirrhosis [9]. Moreover, research showed improved cognitive functions and health-related quality of life in people with cirrhosis with minimal hepatic encephalopathy treated with lactulose [10].

This probably exhausts all the known therapeutic effects of lactulose. Some novelty in this regard has appeared in the work [11]. They wrote that due to fermentation by the bacteria in the gastrointestinal tract, lactulose can produce considerable amount of hydrogen, which is maybe protective for ischemic stroke as a unique antioxidant. These authors supposed that lactulose can induce the production of endogenous hydrogen that in turn reduces oxidative stress and ameliorate the stroke damage in human beings. Based on its own studies, they hypothesize that lactulose may be a novel promising preventive and therapeutic option for stroke as an indirect antioxidant. By increasing gastrointestinal tract derived hydrogen, it may significantly reduce the possibility of stroke and alleviate ischemia/reperfusion injury after the stroke, improving the life quality of patients.

What's more, it is noteworthy that lactulose probably has many other beneficial antioxidant effects on a wide range of aspects, such as cardiovascular diseases, neurodegenerative diseases et al., which still needs further study.

Thus, lactulose is metabolized in the colon by colonic bacteria to monosaccharides, and then to volatile fatty acids, hydrogen, and methane. Volatile fatty acids (VFAs), including acetic, propionic and butyric, are the essential intermediates of anaerobic fermentation. The products of lactulose hydrolysis also include lactic acid. VFAs are

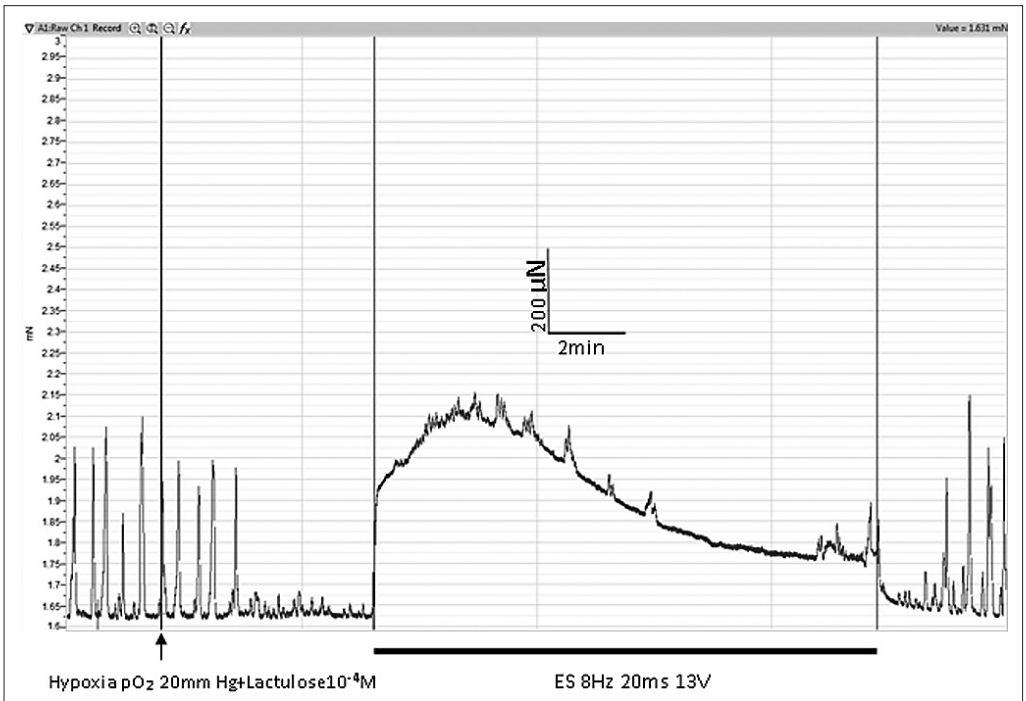

Figure 4. Contractile response of the rat portal vein to field electrical simulation (EC, 8 Hz, 20 ms, 13 V) under hypoxia (20 mm Hg) in the presence of lactulose (10^{-4} M)

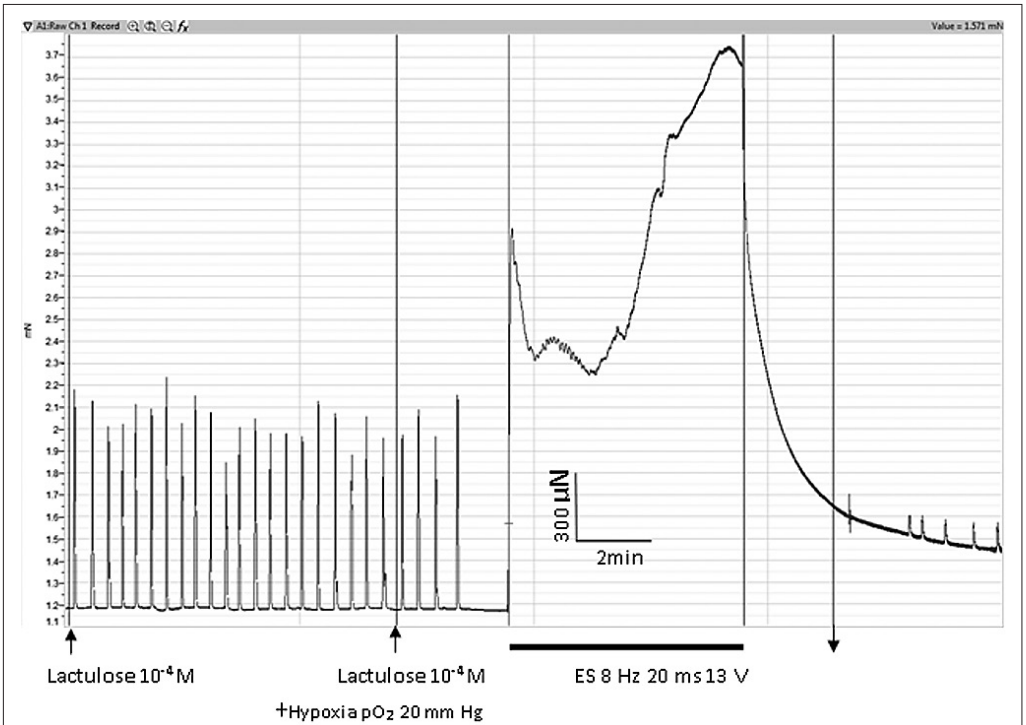

Figure 5. Contractile response of the rat portal vein to field electrical simulation (EC, 8 Hz, 20 ms, 13 V) under hypoxia (20 mm Hg) in the case when the application of lactulose (10^{-4} M) preceded hypoxia

organic compounds with six or fewer carbons in their structure. Although these terms are unfamiliar to the general public, they can be found in nature, usually as a result of bacterial processes such as anaerobic digestion. Given their high energy value, VFAs are a common part of animal metabolism.

Absorption of VFAs at their site of production is rapid, and large quantities are metabolized by the ruminal or large intestinal epithelium of ruminants before reaching the portal blood. Most of the butyrate is converted to ketone bodies or CO_2 by the epithelial cells, and nearly all of the remainder is removed by the liver. Propionate is similarly removed by the liver, but is largely converted to glucose. Although species differences exist, acetate is used principally by peripheral tissues, especially fat and muscle. Significant VFAs, however, are now known to be produced in omnivorous species, such as pigs and humans. Current estimates are that VFA contribute approximately 70% to the caloric requirements of ruminants, such as sheep and cattle, approximately 10% for humans, and approximately 20–30% for several other omnivorous or herbivorous animals. In addition to the energetic or nutritional contributions to the body, the VFAs may indirectly influence cholesterol synthesis and even help regulate insulin or glucagon secretion [12].

The problem is that all this happens in the colon. Doesn't any of this happens in Krebs solution under *in vitro* condition?

In a very useful review [13] clearly indicated that besides glucose, fatty acids also act as an available source of energy for vascular SMCs, and fatty acid oxidation (FAO) generates more energy than glucose, although it needs more oxygen per molecule of ATP synthesized [14]. Fatty acid could change the metabolism of glucose and glycogen in both quiescent and contracting vascular smooth muscle [15]. Porcine carotid arterial segments treated with fatty acid showed suppressed glycolysis and decreased lactate production [16]. In vascular SM, FAO is integrated with glucose metabolism, the energy generated from aerobic glycolysis can be provided by FAO, and the activity of glycolysis can be regulated by the feedback of the products of FAO [16]. During SM phenotype switching, synthetic SM display a decreased glucose oxidation and an increased FAO, and a higher level of FAO may supply further energy for SM to rapid proliferation, migration, synthesis, and secretion of extracellular matrix [17].

The glucose-fatty acid cycle (Randle cycle) is characterized by an alternation between the utilization of glucose and fatty acid, with an increased fatty acid oxidation for ATP production, and, therefore, a blocked glucose oxidation [18]. The Randle cycle was first reported in heart and skeletal muscles and adipose tissues, which play vital roles in the whole-body nutrient homeostasis. Randle cycles also involved in the regulation of cerebral energy homeostasis. However, whether the Randle cycle is engaged in the metabolism of vascular smooth muscle is still unclear.

In the early 90s the data obtained allowed us to suggest that plasma membrane of vascular SM cells and preferentially its Ca^{2+} permeability may be involved in response to hypoxia first of all, and the mechanisms of contractile machinery energy supply take not so great part in this response. This conclusion was based on several lines of evidence. For one, the effects of low pO_2, Ca^{2+} – free solution and Ca^{2+}

channel blockers on SM contractility were very similar. Secondary, inward calcium currents and ^{45}Ca uptake in vascular SM were diminished at hypoxia. Finally, liposomes containing creatine phosphate but not adenosine triphosphate clearly prevented hypoxic vascular relaxation.

This way, our results indicated that one of the most vulnerable links in the chain of excitation-contraction coupling in vascular SM during hypoxia is the system of passive transmembrane Ca^{2+} transport. Inhibition of oxidative phosphorylation induced by oxygen lack is not a limiting factor for energy supply of contractile machinery (at least, during initial steps of hypoxia) but even a little decrease in intracellular creatine phosphate content may lead to decrease of a number of open Ca^{2+} channels resultant from damage in their phosphorylation. Another reason for decrease in Ca^{2+} permeability is a rise in intracellular Ca^{2+} which could be induced by a failure of ATP-dependent Ca^{2+} outward transport and intracellular Ca^{2+} sequestration under hypoxia. Thus, the decrease in Ca^{2+} permeability of SM cell plasma membrane is accompanied by the decrease in Ca^{2+} influx, disturbance in generation of action potentials and phasic contractions and decline in isometric force developed by SM under hypoxia [19].

Hypoxia, as it known, is a condition in which there is a discrepancy between the need for the required amount of oxygen and its supply. Theoretically, a seemingly flawless definition of this condition does not mean that all the fundamental components of its occurrence, development and outcome are well studied and understood. At the same time, the undeniable fact is that drugs that could reduce the negative impact of hypoxia on tissue are urgently needed in clinical practice. Many such compounds are known, which, of course, does not exclude the need to search for new, more effective and safe antihypoxants.

For quite a long time, exogenous glucose was considered an universal antihypoxic agent [20]. However, its antihypoxic effects cannot be explained solely from the standpoint of energy and substrate influence. The fact is that its fluorinated analogue (5-fluoro-deoxyglucose), being metabolized (though more slowly than glucose, but ultimately also to glucose-6-phosphate), aggravates the state of hypoxia [21]. At the same time, fructose also has an antihypoxic effect.

In this regard, we came up with a hypothesis that sugars that are not hydrolyzed by the living cell can have biological effects during hypoxia that are not related to their substrate influence. As an object of study, we settled on the disaccharide lactulose, which contains fructose and galactose connected by a 1-b-4 bond. In the body, outside the intestines, there are no enzymes that could metabolize this bond and hydrolyze this compound. It seems that if lactulose has an antihypoxic effect, this effect will depend exclusively on non-metabolic factors, which would make a significant contribution to the understanding of the fundamental mechanisms of the development of hypoxic conditions.

Carbohydrates are organic compounds composed of carbon, hydrogen, and oxygen atoms. They are typically neutral molecules, meaning they do not carry a net electrical charge. However, in certain biochemical reactions (acidosis due to hypoxia?) carbohydrates can undergo ionization and carry partial charges.

On the other side, channel proteins only move specific substances, which is determined by their charge, size, and

shape. Channel proteins are made from amino acid chains, and the specific sequence of amino acids will determine which molecules a channel can transport. The channel is made from four identical transmembrane subunits, which together form a central pore through the membrane. Negatively charged amino acids are concentrated at the cytosolic entrance to the pore and are thought to attract cations and repel anions, making the channel cation-selective. The voltage-sensing domain of voltage-gated ion channels is a protein structure critical for sensing membrane voltage which is characterized by specific, conserved, and charged amino acid residues. Positively charged residues on ion channel proteins are the main contributors to voltage-sensing and negatively charged residues are believed to participate in this process.

It is usually assumed that molecules are neutral (carry no electrical charges) and do not carry unpaired electrons (all valences are saturated); charged molecules are called molecular ions, molecules with a multiplicity other than unity (that is, with unpaired electrons and unsaturated valences). Thus, under certain changes in environmental conditions (for example, when pH changes), a previously neutral molecule can turn into an electrically charged one and, thus, acquire the ability to interact with a potential sensor in ion channels.

Another aspect of the problem is that carbohydrates are important for protein folding. They are maybe negatively charged and can interact with ion channel amino acid residues or another regulatory protein. For example, expression of functional human CD4 on a surface of T-lymphocytes requires glycosylation of either one or two N-linked sites within the third Ig-like domain. Otherwise the protein is improperly folded and cannot be exported from the endoplasmic reticulum (it is retained there). But there are carbohydrate derivatives that do have ionizable groups, and they would still be considered carbohydrates. For example, glucose 6-phosphate has a charge of about -1.5 at physiological pH, and glucuronic acid would be -1 at physiological pH preventing its diffusion back across the cell membrane into the blood.

Thus, the binding of a carbohydrate molecule to a protein may influence the function of the latter in various ways. Usually one tends to focus on induced conformational changes of the protein. However, though conformational changes may lead to pronounced functional differences, purely electrostatic effects also arise and, in some cases, they may be of more importance than the former (which may not even occur).

It is interesting that even when the carbohydrate does not bear a formal charge, it will change the dielectric environment upon binding since a region previously filled with water (assuming no extensive conformational changes) will be occupied by a much lower dielectric medium. Thus, carbohydrates may act as versatile electrostatic modulators of protein function even when their binding induce few or none conformational changes on the protein molecule [22].

Conclusion

The fact that lactulose has direct antihypoxic abilityis beyond doubt (at least *in vitro*). From a clinician's point of view, this is already good. The compound is well known and absolutely harmless. But pharmacology is the science of the mechanisms of influence of chemical substances on living systems and, therefore, we are obliged to offer such mechanisms. If not absolutely evidence-based, then at least theoretically

acceptable. A possible shift in metabolism toward glycolysis would be a good potential candidate for evidence, but is difficult to substantiate at this time. It remains only to assume the possible interaction of the electrically modified (under conditions of hypoxia and associated acidosis) lactulose molecule with voltage-dependent calcium channels and the restoration of their activity, suppressed during hypoxia.

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Unexpected effects of old drugs – antihypoxic properties of lactulose

Faced with soaring costs of developing new drugs, researchers are looking for ways to repurpose old ones, that is «…the most fruitful basis for discovering a new drug is to start with an old drug». Lactulose is a well-known synthetic sugar used to treat constipation. It is not absorbed in the small intestine and is not broken down by human enzymes. Lactulose is metabolized in the colon by bacterial flora to short-chain fatty acids, monosaccharides, lactic and acetic acids, volatile fatty acids, hydrogen and methane. The problem is that all of this happens in the colon. Could something similar happen in Krebs solution under *in vitro* conditions?

The aim of study – to test experimentally the hypothesis about the possible antihypoxic effect of the drug lactudose *in vitro*.

However lactulose unexpectedly demonstrated a clear ability to restore spontaneous activity of the rat portal vein inhibited under hypoxia *in vitro*. Lactulose effectively restores the amplitude of vascular contractions caused by field electrical stimulation that was inhibited by hypoxia. When lactulose was added to the organ bath both before hypoxic exposure and electrical stimulation, stimulation caused a paradoxical increase in isometric tension.

Preliminary data obtained suggest that the plasma membrane of vascular smooth muscle cells may primarily participate, and the mechanisms of energy supply to the contractile apparatus do not take such a large part in the response to hypoxia. The experiments showed, that one of the most vulnerablel inks in the excitation-contraction coupling chain in vascular tissues during hypoxia is the system of passive transmembrane Ca^{2+} transport.

Probably, sugars that are not hydrolyzed by a living cell can have biological effects during hypoxia that are not related to their substrate influence. As an object of study, we focused on the disaccharide lactulose, which contains fructose and galactose. In the body, outside the intestines, there are no enzymes that could metabolize this bond and hydrolyze this compound. It seems that if lactulose has an antihypoxic effect, then this effect will depend exclusively on non-metabolic factors, which will make a significant contribution to the understanding of the fundamental mechanisms of the development of hypoxic conditions. The voltage-sensing domain of voltage-gated ion channels is a protein structure important for membrane voltage sensing that is characterized by specific, conserved, and charged amino acid residues.

It is generally assumed that molecules are neutral and do not carry unpaired electrons. Charged molecules are called molecular ions, molecules with a multiplicity other than unity (i. e., with unpaired electrons and unsaturated valences). Thus, under certain changes in environmental conditions (for example, a change in pH), a previously neutral molecule can become electrically charged and thus acquire the ability to interact with a potential sensor in ion channels. Interestingly, even if a carbohydrate does not carry a formal charge, when bound it will change the dielectric environment, since the region previously filled with water (in the absence of significant conformational changes) will be occupied by an environment with a much lower dielectric constant. Thus, carbohydrates can act as universal electrostatic modulators of protein function, even if their binding causes little or no conformational change in the protein molecule.

In conclusion, it should be noted, the fact that lactulose has antihypoxic properties is beyond doubt. From a clinician's point of view, this is already good. The compound is well known and completely harmless. But pharmacology is the science of the mechanisms of action of chemicals on living systems, and therefore we are obliged to propose such mechanisms. If not absolutely demonstrative, then at least theoretically acceptable. A possible metabolic shift towards glycolysis would be a good potential candidate for evidence, but is currently difficult to substantiate. It remains only to assume the possible interaction of the electrically modified (under conditions of hypoxia and associated acidosis) lactulose molecule with voltage-dependent calcium channels and the restoration of their activity, suppressed during hypoxia.

Key words: drugs, lactulose, antihypoxic properties

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Несподівані ефекти старих ліків – антигіпоксичні властивості лактулози

Зіткнувшись зі стрімкими витратами на розробку нових ліків, дослідники шукають шляхи перепрофілювання старих, тобто «…найпліднішою основою для відкриття нового препарату є почати зі старого препарату». Лактулоза – це добре відомий синтетичний цукор, який використовується для лікування запорів. Він не всмоктується в тонкому кишечнику та не розщеплюється ферментами людини. Лактулоза метаболізується в товстій кишці бактеріальною флорою до коротколанцюгових жирних кислот, моноцукрів, молочної та оцтової кислоти, летких жирних кислот, водню та метану. Проблема в тому, що все це відбувається в товстій кишці. Чи може щось подібне статися у розчині Кребса в умовах *in vitro*?

Проте лактулоза несподівано продемонструвала чітку здатність відновлювати спонтанну активність воротної вени щурів, пригнічену за умов гіпоксії *in vitro*. Лактулоза ефективно відновлює амплітуду пригнічених гіпоксією судинних скорочень, викликаних польовою електростимуляцією. Коли лактулозу додавали до перфузату перед гіпоксичним впливом й електричною стимуляцією, стимуляція викликала парадоксальне збільшення ізометричного тонусу.

Мета дослідження – експериментальна перевірка гіпотези про можливу антигіпоксичну дію препарату лактудози *in vitro*.

Отримані попередні дані свідчать про те, що у відповідь на гіпоксію перш за все може брати участь плазматична мембрана гладеньком'язових клітин судин, а механізми енергозабезпечення скорочувального апарату не впливають настільки значно на цю реакцію. Отримані результати показали, що однією з найвразливіших ланок ланцюга зв'язку збудження-скорочення в тканинах судин за гіпоксії є система пасивного трансмембранного транспорту Ca^{2+}.

Імовірно цукри, які не гідролізуються живою клітиною, можуть мати біологічні ефекти за умов гіпоксії, що не пов'язані з їхнім впливом на субстрат. Як об'єкт дослідження було обрано дисахарид – лактулозу, що містить фруктозу та галактозу. В організмі, поза кишечником, немає ферментів, які могли б метаболізувати цей зв'язок і гідролізувати сполуку. Здається, якщо лактулоза має антигіпоксичну дію, то ця дія залежатиме виключно від неметаболічних факторів, що зробить значний внесок у розуміння фундаментальних механізмів розвитку гіпоксичних станів. Потенціалчутливий домен потенціалзалежних іонних каналів – це білкова структура, що важлива для сприйняття мембранної напруги та характеризується специфічними зарядженими амінокислотними залишками.

Зазвичай вважається, що молекули нейтральні та не несуть неспарених електронів. Заряджені молекули називаються молекулярними іонами (тобто, з неспареними електронами та ненасиченими валентностями). Таким чином, за певних змін умов навколишнього середовища (наприклад, pH) раніше нейтральна молекула може стати електрично зарядженою й таким чином набути здатності взаємодіяти з датчиком потенціалу в іонних каналах. Цікаво, що навіть якщо вуглевод не несе формального заряду, коли він зв'язаний, то здатен змінити діелектричне середовище, оскільки область, яка раніше була заповнена водою (за відсутності значних конформаційних змін), буде зайнята середовищем зі значно нижчою діелектричною константою. Таким чином, вуглеводи можуть діяти як універсальні електростатичні модулятори функції білка, навіть якщо їхнє зв'язування викликає незначні конформаційні зміни в молекулі білка або взагалі не викликає їх.

Таким чином, слід зазначити той факт, що лактулоза має антигіпоксичні властивості, не викликає сумнівів. З точки зору клініциста, це вже добре. Сполука добре відома й абсолютно нешкідлива. Але фармакологія – це наука про механізми дії хімічних речовин на живі системи, і тому ми зобов'язані запропонувати такі механізми. Якщо не абсолютно показові, то принаймні теоретично прийнятні. Можливий метаболічний зсув у бік гліколізу був би хорошим потенційним кандидатом для доказів, але наразі його важко обґрунтувати. Залишається тільки припустити можливу взаємодію електрично модифікованої (в умовах гіпоксії та пов'язаного з нею ацидозу) молекули лактулози з вольтаж-залежними кальцієвими каналами та відновленням їхньої активності, яка пригнічена під час гіпоксії.

Key words: ліки, лактулоза, антигіпоксичні властивості

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