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Morphofunctional traits and reactivity of the portal vein

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Abstract

Background: Portal vein is the most enigmatic vessel of our body because it regulates own contractile performances using a special pace-maker mechanism represented by cells of Cajal. The contribution of various metabolic mediators and natural vasotropic agents in the control of the portal blood circuit is much less studied compared to the arterial system in general and the hepatic system in particular. The studies designed on the structure, function, and reactivity of the portal vein in different preconditioning have brought some common but also distinct evidence of the arterial system. Nitric oxide production is higher partly due to reduced arginase expression, but muscular media is thinner. Periodic spontaneous contractions directed towards the liver gate are characteristic for portal vein (PV), and the longitudinal muscle fibers are considered to be responsible for this phenomenon. Spontaneous rhythmic oscillations of the cells of Cajal are triggered by increasing calcium ion concentration leading to their depolarization. PV constrictor effect of phenylephrine is dependent on the activity of receptors to ET-1. For PV is characterized the acetylcholine induced contraction either *in vivo* or *in vitro*, and this effect is thought to be dependent on ET-1.

Conclusions: The establishment of main particularities of portal vein reactivity of action of different paracrine, endocrine, and hemodynamical stimuli represents an important tool for prediction of contractile disorders leading plausible to portal hypertension. Likewise, a well proven interplay between cholinergic and adrenergic stimulations and on the other hand between Ang II and ET-1 actions must be a support for pharmacological modulating of portal vein reactivity disorders.

Key words: portal vein, morphofunctional traits, vein reactivity.

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Introduction

Portal vein is the most enigmatic vessel among vascular bed at least due to a unique capacity to realize a rhythmic spontaneous contraction so needed for a normal blood influx into the liver. Likewise, portal vein consists of a lot of receptors placed on both sensorial layers of the wall, endothelium, and muscular media, being high receptive to action of cholinergic and adrenergic natural stimuli, of Ang II, ET-1 and other vasoactive peptides and oligopeptides. The complex response of portal vein on neuroendocrine and hemodynamical signals mediated basically by calcium ions, nitric oxide, cAMP, and cGMP should complete and synchronize the spontaneous pace-maker-induced contraction in order to ensure an adequate blood pressure of about 10 mm Hg, capable to reach a suitable gradient of pressure between vena cava inferior and vena portae.

Morphofunctional traits of the portal vein

The portal vein (PV) provides 75% of blood flow to the liver anatomically positioned in the gastrohepatoduodenal ligament adjacent to the hepatic artery, which brings the last quarter of blood to the liver parenchyma by confluence of 3 big veins: gastric, splenic, and superior mesenteric. In the adult human body, the PV has an average length of 7-8 cm and a diameter of about 10 mm, and before entering the liver it ramifies into 2 branches: left and right. The role of PV in the body's homeostasis is notable, given the fact that it ensures the liver's access to the nutrients and metabolites of gastrointestinal digestion necessary for normal liver function, and on the other hand, it ensures the influx of metabolic toxins for the body's purification consistent with detoxification. The share of blood used by the liver from the general circulating minute volume is about 25%, so PV compliance in this context is announced as an important arrangement in view of the fact that hepatocytes are the cells with the highest level of perfusion [1]. At the same time, the blood stored in the liver can be an important element engaged in the cardiovascular mechanisms to compensate for fluid losses and dehydration of the body. Even a moderate elevation of PV pressure above the normal value (7-10 mm Hg) leads to increased PV/inferior vena cava pressure gradient (maximum value = 5.0 mm Hg) or an increase >6.0 mm Hg vs. of the right atrium and, respectively, at the risk of peripheral hemodynamics: from the risk of congestion and transudation in the abdominal cavity to the constriction of the renal arteries [2, 3]. The latter phenomenon is detected in the hepato-renal syndrome, which is triggered in the liver, when the portal blood flow

is compromised and associated with an increase in adenosine concentration, reflexively causing the activation of the renal sympathetic system, the release of renal vasoconstrictor agents and, respectively, constriction of the renal arteries [4]. Therefore, the feasibility of PV is orchestrated by a multifactorial system that is based on the conclusive cooperation between vegetative influences and humoral factors with paracrine and endocrine action.

The portal vein has sympathetic and parasympathetic innervations, the proximal mediators being involved in the regulation of basal vascular tone. Vegetative innervations are also common for the hepatic artery and bile ducts. Postganglionic sympathetic nerve fibers originate from the superior mesenteric and celiac ganglia, which in turn receive preganglionic fibers from the T7-T12 spinal ganglion. Parasympathetic fibers have a vagal origin and, similar to sympathetic ones, are involved in controlling the activity of paravascular liver neurons under the action of osmotic and metabolic stimuli, which send efferents to the main centers of the brain [5]. Recent reports indicate the role of the imbalance between sympathetic and parasympathetic influences with the predominance of adrenergic stimuli not only in affecting basal vascular tone, but also in hepatic metabolic disturbances, primarily carbohydrate and lipid [6]. Remarkably, the value of the ratio of sympathetic and parasympathetic nerve endings in the PV is dependent on the phenotype of the mammal, but it is normally accepted that the density of parasympathetic fibers predominates, their effects being, however, closely related to the functionality of the vascular endothelium. The increase in sympathetic activity in the regulation of PV tone or the impairment of parasympathetic control are estimated as trigger factors of the elevation of portal venous pressure, as well as intrahepatic vascular resistance in the arterial system inherent in various chronic liver diseases. J. Van Limmen et al. (2022) demonstrated that the sympathetic mediator, norepinephrine, is the cause of the reduction in portal blood circulation and hepatic arterial flow, an effect mediated by α1-adrenergic receptors expressed on vascular smooth myocytes [7].

The contribution of various metabolic mediators and natural vasotropic agents in the control of the portal blood circuit is much less studied compared to the arterial system in general and the hepatic system in particular. Under this aspect, the importance of highlighting the particularities of PV reactivity to the action of adenosine, acetylcholine, bradykinin, endothelin-1 (ET-1), angiotensin II (Ang II), adenosine triphosphate (ATP), lactate, pyruvate, is addressed. The regulation of the basal tone of the PV occurs under conditions different from those of the vascular zones, since the toxic substances of the portal system, after being metabolized in the liver, have an independent vasoconstrictor or relaxant action, a fact that interferes detrimentally with the intrinsic control system of compliance and portal pressure. In addition, the physiological entity of the "hepatic vascular buffer" system imposes in conditions of reduced blood flow to the liver via the hepatic artery (e.g., in atherosclerosis, stenosis, thrombosis) the increase of the portal circuit due to the dilatation of the PV, in order to maintain the adequate perfusion of the parenchyma. Accordingly, the presence of a liver ischemia signaling system intended to induce the dilation of the portal vein commensurate with the constriction of the hepatic artery, primarily through paracrine actions, is appropriate in this regard. The inverse relationship is also plausible, i.e., relaxation of the hepatic artery under conditions of increased portal pressure caused by exaggerated contraction of PV smooth myocytes. At present, the regulatory mechanisms of the "hepatic vascular buffer" system are apocryphal and require further elucidation. The research designed on the structure, functionality, and reactivity of the portal vein in different preconditioning have brought some common but also distinct evidence of the arterial system.

First of all, the vascular endothelium represents, as in the arteries, a single layer of cells that, beyond the mechanical barrier, performs important homeostatic functions. The capacity of the venous endotheliocyte to synthesize nitric oxide is higher compared to that of the arteries. This is due to the higher expression of endothelial nitric oxide synthase (eNOS) and in part to the reduced expression of arginase that engages the NO substrate (L-arginine) in the ornithic cycle. Regarding the contribution of the venous endothelium in the control of hemostasis, it should be noted that the expression of thrombomodulin, antithrombin III, as well as the receptors of the annexin-5 family compared to the anticoagulant protein C is estimated at similar levels to the arterial segment. At the same time, the expression of endothelial receptors for von Willebrand factor is considered to be lower, since the pro-coagulant pentamer in the smooth venous circuit does not discover all 5 ligand sites similar to arteries.

Second, the muscular media of the venous wall is thinner, and the elastic laminae that separate the intima (i.e., internal elastic lamina) and adventitia (i.e., external elastic lamina) media are missing. Smooth myocytes are numerically depleted and arranged centrally and longitudinally circularly, which are placed in the square of the circular ones or outside them. The muscular media of the arteries does not contain longitudinal muscle fibers. In the veins of the lower limbs, the structural arrangement of the muscular media excels through the formation of the valvular apparatus. The ratio of type I fibrillar collagen to type III in the extracellular matrix (ECM) inherent in the muscle medium is higher versus the index characteristic of arteries, which is in an agreement with the much higher compliance of veins. The expression of type IV reticular collagen is considerably reduced with the lack of elastic membranes. The adventitia has a composition similar to arteries and contains fibrillar collagen fibers, elastic fibers and all the cells of the MEC: fibroblasts, mast cells, macrophages.

The structure of the rat portal vein is better studied. The results obtained brought to highlight some significant features [8, 9]:

The endothelial layer of the extrahepatic segment of the PV has folds, which anatomically correspond to the areas of the venous wall containing well-developed longitudinal muscle fibers. Thus, it is suggested that the latter participate in the formation of endothelial folds. Endothelial cells are arranged between the folds of the intima in a circumflex fashion. This finding indicates that circumferential blood flow occurs locally on the luminal surface between the intimal folds. Endothelial cell alignment is determined by periodic mechanical loading, which in turn is contiguous with circular and longitudinal myocyte contraction. In the conditions when the endotheliocytes in the cell culture are exposed to periodic stretching and relaxation, then their long axis is reoriented perpendicular to the extension force. Such an orientation of the endothelial cells ensures *in vivo* a greater resistance against periodic mechanical stress and, therefore, a minimal deformation of the cell unit. Intimal folds in rats are circumflex and arranged parallel to each other.

Periodic spontaneous contractions directed towards the liver gate are characteristic for PV, and the longitudinal muscle fibers are considered to be responsible for this phenomenon, attested in several types of mammals (rodents, cats, rabbits, guinea pigs, etc.). The contraction of the longitudinal muscle fibers is stronger in the distal segment and decreases towards the liver gate, and the intima with circularly arranged endothelial cells is less exposed to tension and stretching stress.

Longitudinally arranged smooth myocytes are exposed in the outer zone of the PV wall, and circumflex myocytes – in the inner zone. These 2 types of myocytes have distinct contributions to the overall mechanical activity of the portal vein. The longitudinal myocytes are meant to counteract the gravitational force of the blood, and the contraction of the circumflex myocytes relieves the hydrostatic pressure of the blood. Remarkably, the elevation of the hydrostatic pressure of the blood during the postnatal period of body development leads to the more pronounced development of the circumflex smooth myocytes compared to the longitudinal fibers. It is also worth paying attention to the fact that in the proximal segment the ratio of circumflex myocytes to longitudinal cells is higher compared to the distal segment of the portal vein. In the proximal segment of the PV the hydrostatic pressure of the blood is obviously higher versus the distal segment.

The periodic spontaneous contractions of the portal vein are corroborated to be triggered and controlled by cells of Cajal, the presence of which was initially proven in the rabbit portal vein in the area of the muscular media and reported in 2004 by M. Harhun et al. [10]. By applying confocal microscopy and electron myography, the connection of these cells with smooth myocytes of the PV was established. Spontaneous rhythmic oscillations of cells of Cajal were triggered by increasing calcium ion concentration leading to their depolarization. Conceptually, it is important to mention that the depolarization of the smooth myocyte occurred at a distance of about 4 sec after the depolarization of the Cajal's cell. At the same time, the depolarization of the adjacent Cajal's cell was followed, only much faster: after about 200 msec. Thus, it was rightly concluded that the Cajal's cell can serve as a pacemaker of the muscle medium of the PV, and the depolarization of the smooth myocyte can be not only the repercussion of the electrical contact between them, but also the result of the action of some mediators released by the Cajal's cell able the induce depolarization of the adjacent myocyte.

Although discovered precisely in 1889 by the Spanish specialist in neuroanatomy, Santiago Ramon Cajal, these cells that bear his name (i.e., cells of Cajal) have remained an enigma to this day in terms of their functional role in various vital organs. Being abundantly detected in the gastrointestinal tract, their removal led to the disappearance of the slow depolarization wave of intestinal smooth myocytes, including under conditions of electrical stimulation. For a long time, experimental research could not highlight the mechanisms of the pacemaker activity of Cajal's cells, and the accumulated evidence points to the role of calcium unloading from the endoplasmic reticulum of the smooth myocyte, the activation of L-type channels in the myocyte membrane (the second source of calcium during of depolarization) and/or activation of Na-K membrane pumps.

The morphological remodeling of the portal vein, a ubiquitous phenomenon in portal hypertension, manifests itself through notable structural and geometric changes especially in the intima and the muscular media, which result in endangering the reactivity of the vein to the action of various natural stimuli. C. Ho et al. (2019) demonstrated that hypercholesterolemia and elevation of the circulating level of oxidized low-density lipoproteins are imposed by endothelial damage of the PV and its inflammation in association with the formation of imminent atherosclerosis plaques against the background of increased serum content of pro-inflammatory interleukins in patients with fatty infiltration of the liver [11]. Endothelial injury resulted in portal hypertension with detrimental effect on liver perfusion. At the same time, it is admitted that PV remodeling is accompanied by a decrease in the population of Cajal's cells due to the activation of their apoptosis induced by inflammatory mediators (extrinsic pathway of apoptosis induced by TNF-α), oxygen free radicals, energy deficit (intrinsic or mitochondrial pathway induced by cytochrome C) or their differentiation under the action of the same factors [12]. Portal vein endothelium controls circumflex and longitudinal smooth myocyte functionality via endothelial derivatives, NO and prostacyclin or prostaglandin I2 (PGI2). M. Trindade et al. (2017) demonstrated in cell culture experiments that the basal level of NO in PV endotheliocytes is similar to the characteristic index of inferior vena cava endotheliocytes, but incubation of the culture with ET-1 did not increase NO expression in PV, unlike the incremental response [13]. On the other hand, the basal level of PGI2 in PV endotheliocytes was significantly higher compared

to that in the inferior vena cava, but analogously to the change in NO, incubation of the culture with ET-1 was not imposed by increasing prostacyclin production, contrary to caval endotheliocytes. So, the endothelium of the portal vein is functionally marked by notable particularities, which can be important landmarks regarding its reactivity in different hemodynamic, paracrine, and neuroendocrine preconditioning. The PV endothelium expresses different types of receptors, the activation of which promotes the contraction and relaxation of the muscular media, consequently determining the reduction or increase of blood flow to the liver. Currently, the presence of the following types of receptors is proven, the expression of which is dependent on the phenotype of the mammal:

- Muscarinic type 1 and 3 (M1 and M3) to acetylcholine. The presence of M5 receptors is also indicated in rabbits.
- H1 to histamine (their expression in rat VP is low).
- ETB to endothelin 1.
- Alpha 2 adrenergic to norepinephrine (NE).
- AT2 to Ang II.
- Receptor mass to angiotensin 1-7.
- VIP2 to vasoactive intestinal peptide (VIP)
- B2 to bradykinin.

The effect of stimulating these receptors is in direct correlation with the ability of the PV endotheliocyte to release NO or PGI2, and in liver dysfunction their share and, respectively, the final effect can be notably influenced. Thus, I. Bockh et al. (2011) demonstrated in situ in rats with portal hypertension that stimulation of the hepatic branch of the vagus nerve with the frequency of 5 Hz decreased the value of hypertension against the background of increasing the concentration of acetylcholine in the portal circuit [14]. Pretreatment of animals with L-NAME (eNOS inhibitor) abolished the vagal effect on portal hypertension, a fact indicating the role of NO in promoting the cholinergic effect. Vagal stimulation with a double frequency (i.e., 10 Hz) led to an increase in the concentration in the portal circuit of vasoactive intestinal peptide also associated with a reduction in portal hypertension, an effect that was not abolished by the administration of L-NAME, but impaired in pretreatment with the blocker VIP2. Of note, both mediators of vagus nerve stimulation decreased intrahepatic vascular resistance, an important mechanism of portal hypertension. Therefore, vagus nerve stimulation may be an opportunity for pathogenetic treatment of portal hypertension and its impending consequences.

The portal vein smooth myocytes express the following receptors:

- M2 to acetylcholine. Their stimulation by acetylcholine produces contraction of smooth myocytes.
- ETA and ETB in distinct proportion in different mammals, but with notable superiority of ETA receptors: from 5:1 to 8:1. Remarkably, ET-1 is an important factor in the evolution of liver fibrosis, leading to increased hepatic vascular resistance and portal hypertension, respectively. ETA receptor antagonists improve both liver parenchymal remodeling and portal vein reactivity.
- AT1 to Ang II.
- Alpha 1 adrenergic to NE.
- Beta 2 adrenergic to epinephrine.
- H2 to histamine.

Activation of the majority of receptors expressed by smooth myocytes of the PV triggers and supports the remodeling process of the wall of the portal vein, which accelerates and facilitates the evolution of portal hypertension. In this context, the role of the TMEM16A protein in promoting the proliferative and growth effects of ET-1 and Ang II, the main vasotropic factors involved in the control of portal vein functionality, is important [15, 16].

Integrins, syndecans and alpha-dystroglycans are receptors of smooth myocytes of the PV, whose role in the remodeling of the portal vein is targeted through the prism of controlling the contractile phenotype of the muscle cell. Their activity is considered to be in tune with the functionality of aldosterone receptors, the stimulation of which stimulates the expression of MEC fibroblasts and the exaggerated synthesis of type I and type III fibrillar collagen. The impact of aldosterone on vein remodeling is estimated to be below the hormone's impact on arteries and myocardium at least because of the lower expression of the receptor in veins.

In vitro reactivity features of the portal vein

Adequate control of blood flow to the liver through the portal vein requires a feasible system to regulate reactivity to various paracrine and neuroendocrine actions, accomplished in contiguity with the property of the portal vein to spontaneously contract due to the presence of Cajal's pacemaker stromal cells. The response of the portal vein significantly influences the evolution of portal hypertension in view of the fact that a blood congestion caused by venous dilatation is a factor facilitating the formation of esophago-portal and gastro-portal anastomoses and the risk of their consequences. Fundamental research carried out *in vitro* on isolated rings or strips of portal vein taken from different laboratory animals is the main lever for studying the peculiarities of the response of the vein exposed to the action of a wide range of natural agents with physiological and pathological action, pharmacological substances, variations in concentration of ions, etc. The basic components of the experimental protocols involve estimations of the response of the portal vein to cholinergic, adrenergic, Ang II, ET-1, vasopressin actions, extra- and intracellular changes in the concentration of calcium, magnesium, sodium, potassium, pH value, etc.

Any experiment begins with the attestation of the spontaneous contraction of the portal vein caused by the cells of Cajal and which is imposed by the amplitude and frequency of the contraction depending on the phenotype of the laboratory animal. The presence of these spontaneous contractions indicates a sampling of bands or isolated rings without traumatizing elements, as well as the feasibility of

Krebs perfusion solution. In a recent publication W. Al-Aghawani (2022) demonstrated in this context the spontaneous phasic rhythmic contractions of the portal vein benzo taken from Sprague Dawly rats with the respective amplitude and frequency values [17]. The action of phenylephrine added to the infusion solution up to a concentration of 10-6 M obviously led to an increase in both contraction amplitude and frequency. The constrictor plateau induced by phenylephrine and which is mediated by the activation of α1-adrenergic receptors expressed on smooth myocytes is used as a benchmark to estimate the effect of agents with vasorelaxant action.

A. Chies and P. Rossignoli demonstrated that the constrictor effect of phenylephrine is dependent on the activity of receptors to ET-1, thus, premedication of the isolated portal vein with antagonists of ETA and ETB receptors (e.g., BQ-123 and BQ-788) decreased amplitude of adrenergic contraction [18]. A similar contractile impairment was detected in the denuded portal vein model, given that the endothelium is the main source of ET-1 synthesis, and inhibition of eNOS by L-NAME did not alter the contraction of the portal vein with intact endothelium consistent with the action of phenylephrine.

The portal vein, like the arteries, is influenced by hemodynamic stress, which triggers the process of vascular remodeling, which in the context of the venous wall is conclusively based on the proliferation of smooth myocytes. The evolution of portal vein remodeling against the background of portal hypertension is associated with increased ET-1 production and the expression of specific receptors ETA and ETB in tune with the activation of the respective endotheliocyte genes, including the genes responsible for NO production. Nitric oxide released into the wall of the portal vein is intended to counteract the effect of ET-1 in stimulating the proliferation of smooth myocytes and endotheliocytes. In the arterial wall, NO released in excess in hemodynamic stress also serves to counteract the vasoconstrictor effect of ET-1.

In the arteries, NO production is much more pronounced under hemodynamic stress, compared to the portal vein. With this connotation, the hypothesis based on the data obtained in the research of the portal hypertension model reproduced in pigs and rats is important, that the evolution of the remodeling of the portal vein is imposed by the more significant increase in the production of NO, a phenomenon defined as "venous arterialization" [19]. Its presence in the context of portal hypertension and remodeling of the portal vein has notable repercussions, first of all the dilation of the mesenteric veins and the increase of venous inflow in the portal vein, which will accentuate the portal hypertension and the remodeling of the portal vein, and on the other hand it will increase the venous congestion important in the formation esophago-gastro-portal anastomosis. What are the molecular mechanisms supporting the activation of genes that may be involved in the genesis of the phenomenon of "venous arterialization" remain complicated even now. Increased insulin-like growth factor receptor expression is suggested to be inherent in the process of venous remodeling associated with the progression of portal hypertension.

The potentiation of the vasoconstrictor and vasorelaxant response detected in portal hypertension understandably addresses the particularities of the adrenergic, angiotensin, endothelin and vasopressin reactivity of the portal vein in connection with the cholinergic response. Activation or inhibition of alpha1-adrenergic receptors results in changes in the expression and affinity of muscarinic (M3) receptors, which mediate the action of acetylcholine. Moreover, it is characteristic of the portal vein to change the activity of beta-adrenergic receptors in the context of blocking alpha-adrenergic receptors and vice versa.

Regarding the effect of cholinergic stimulation on the reactivity of the hepatic veins and the extrahepatic portae system, the data obtained *in vivo* demonstrated that the administration of acetylcholine leads to venous constriction, an effect dispensable by the action of atropine, but annihilated by phentolamine. This effect was also confirmed *in vitro*, being suggested that acetylcholine stimulates the synthesis and release of the constricting endothelial factor, ET-1, an effect plausibly mediated through nicotinic receptors, as their blockade by tubocurarine diminishes the constricting effect of acetylcholine on isolated rings of the portal vein.

There are solitary reports of the action of other members of the endothelin family (e.g., ET-2 and ET-3) on the response of the portal vein. Thus, both ET-2 and ET-3 have been shown to induce contraction of isolated rings of the portal vein and potentiate spontaneous contractility in a manner dependent on the concentration of oligopeptides in the perfusate, but in proportion underlying the effect of ET-1. The constrictor effect of ET-1 was stronger compared to that of bradykinin, Ang II, phenylephrine, thromboxane A2 (TxA2), and substance P, but underlying the constrictor plateau induced by depolarization with 80 mM KCl solution. The gradual reduction of the calcium ion concentration to zero caused the decline of the constrictor plateau, but not to the isoline, which was recovered with the addition of the cation in the Krebs infusion solution, a fact that confirms the role of extracellular calcium in the endothelin contraction of the portal vein and, in part, of intracellular Ca. L-type Ca channels have a significant role in promoting ET-1-induced contraction, but not the ultimate one, as their blockade with Nicardipine did not completely abolish the constrictor response. Blockade of T-type calcium channels by NiCl2 reduced the constrictor plateau more considerably compared to Nicorandine, but also the annihilation of the response was relative. Therefore, these results highlight the role of both types of calcium channels (L- and T-type) in achieving the contraction of the portal vein under the action of ET-1, which is released from the endothelium, but also record the input of other calcium channels, such as would be receiver-controlled channels and/

or non-selective channels. Regarding the release of ET-1 in the stimulation of the vessel with acetylcholine, it is important to mention that hypoxia and acidosis are factors that increase the endothelial production and release rate of ET-1, a fact that can significantly influence the reactivity of the cholinergic portal vein. Regarding the role of intracellular calcium in promoting the constricting effect of ET-1, the ability of the oligopeptide to stimulate phospholipase C and trigger the phosphoribosyl cascade mediated by prokinase-C, and IP3 and the resulting diacylglycerol mobilize calcium from the sarcoplasmic reticulum.

PV muscular media depolarization by ET-1 followed by extracellular calcium influx is evidenced by the fact that activation of K-ATP-dependent channels by Cromakalim, resulting in hyperpolarization of the muscle medium, prevented contraction of the rat portal vein. At the same time, the hyperpolarization of the smooth muscles did not abolish the constrictive effect of ET-1 on the portal vein in the absence of calcium in the perfusate, which justifies the feasibility of the constrictive mechanism of ET-1 linked to the IP-3/diacylglycerol system. It should be noted that a similar effect of Cromakalim was also obtained on isolated human portal vein [20]. The contribution of K_{ATP} channels in the control of smooth muscle reactivity proven in research on the rat portal vein is also confirmed on the pig detrusor muscle, a fact that substantiated the development of pharmacological remedies with a relaxing effect on the smooth muscles through the hyperpolarization mechanism.

The connection between K_{ATP} channels and the action of ET-1 is also claimed by the fact that blockade of these channels by Glimenclamide not only annihilates the vasorelaxant effect of Cromakalim but potentiates ET-1-induced contraction of the portal vein. Similar effect of K_{ATP} channel activation on portal vein reactivity to ET-1 action was also found in adrenergic stimulation with phenylephrine. Furthermore, removal of calcium from the Krebs perfusate abolished the impending contraction of the action of the alpha-1 adrenergic receptor agonist, phenylephrine, on isolated rings of the portal vein (fig. 1).

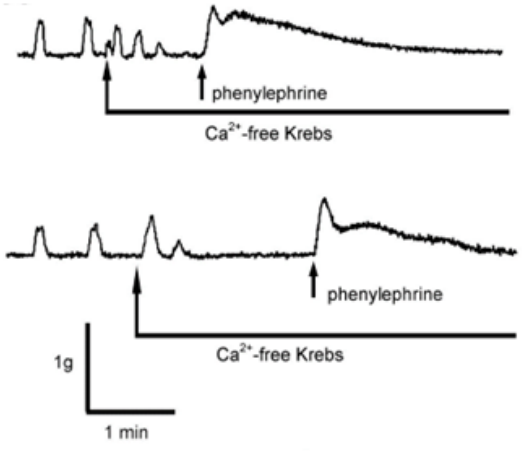

Fig. 1. Effect of phenylephrine on contraction of portal vein perfused without calcium [21]

Adrenergic and endothelinic contraction of the portal vein is naturally counteracted by nitric oxide, the level of which in reproduced portal hypertension in rats has been shown to be significantly elevated compared to intact animals. The contractile effect of phenylephrine (0.1 mM) and KCl solution (10-80 mM) was diminished relative to the reference pattern. The concentration of KCl solution required to induce ½ of the maximum contractile plateau of isolated rings by the depolarizing mechanism was significantly higher.

Thus, under the prism of the exegesis of the role of NO in promoting the reactivity of the portal vein, 2 important cardinal aspects are announced:

(1)- NO released by eNOS, as well as exogenous NO released in nitrate metabolism (e.g., sodium nitroprusside) diminishes the constrictor plateau induced by phenylephrine and ET-1.

(2)- Acetylcholine, although it stimulates eNOS to produce NO, induces contraction of the portal vein, an effect partly dependent on the stimulation of the endothelium to release ET-1. Denudation of the portal vein reduces the contractile activity of acetylcholine, which demonstrates the superiority of the ET-1 mechanism in promoting cholinergic reactivity over the NO mechanism.

These inherent subtleties are important in explaining the evolution of portal hypertension related not only to the increase in hepatic vascular resistance (e.g., inflammation, fibrosis, cirrhosis, etc.), but also to the peculiarities of the response of the portal vein, as well as in the development of the prevention of the clinical manifestations which are characteristic for portal hypertension. The main causes of increased circulating NO levels in portal hypertension are not fully established. The role of neuroendocrine activation in liver diseases is assumed, which increases the amplitude of hemodynamic stress, which results in increased eNOS expression, as well as increased inducible NOS (iNOS) expression against the background of increased inflammatory response and oxidative stress.

L. Caracuel et al. (2019) demonstrated an increased capacity of NO production and arterial endothelium, in the context of phenylephrine stimulation of the isolated rat mesenteric artery with acute or chronic liver disease [22].

There are reports calling for the ability of the vascular endothelium to synthesize and release ad-luminal and ab-luminal manner not only ET-1, but also catecholamines, norepinephrine, and epinephrine. Their autocrine and paracrine action on the cells of the vascular wall triggers the exaggerated production of oxygen free radicals, which results in the premature metabolism of NO and the increase in the expression of pro-inflammatory cytokines [23, 24]. Cumulatively, these factors alter the vascular reactivity of both arteries and veins.

Under the hood of the importance of the reactivity of the portal vein in the evolution of portal hypertension and its clinical manifestations, the effect of different morphofunctional improvement remedies of the liver or other consumed substances on the motor activity of the vein

must also be addressed. Thus, the caffeine found in coffee is interesting in this context, given its beneficial action on liver fibrosis and cirrhosis by stimulating angiogenesis, mitigating oxidative stress and inflammatory mediators. Basic research has demonstrated that caffeine induces contraction of isolated rings of the portal vein, engaging in exercise both the intracellular calcium stored in the sarcoplasmic reticulum (SR) and the extracellular cation [25]. Blocking the ryanodine receptors expressed on the SR leads to the annihilation of 35-40% of the phasic contractions induced by caffeine, which proves that by activating these receptors, caffeine produces the release of calcium from the SR deposits. Evidence of the role of extracellular calcium is the progressive reduction of the plateau constrictor of the isolated rings of the portal vein induced by caffeine in their perfusion with the reduced concentration of calcium or in conditions of premedication with calcium antagonists (fig. 2).

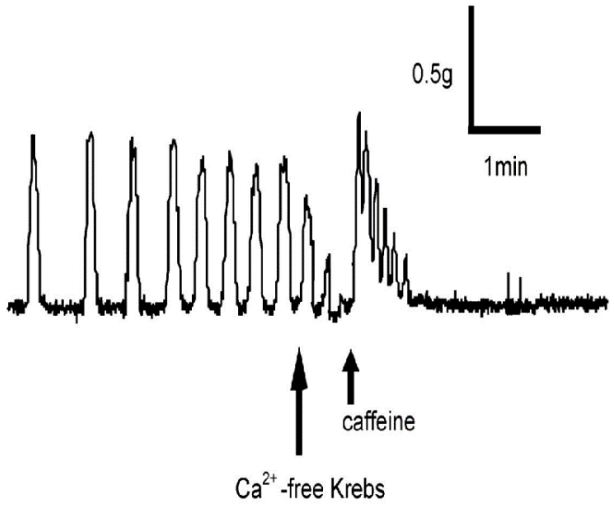

Fig. 2. Effect of caffeine on contraction of portal vein perfused without calcium [21]

Under conditions of perfusion of isolated rings of the portal vein with increased concentrations of potassium, caffeine produces only a contraction that quickly extinguishes. In high concentrations, the potassium in the perfusate (20-100 mM) produces the phasic contraction of the portal vein due to the depolarization of the vascular smooth myocyte. It is important to note that this depolarization consistent with excess potassium produces a short-term phasic contraction of the portal vein, even in conditions of lack of calcium in the perfusate, a fact that indicates the direct action of depolarization on the release of calcium from the SR. Activation of potassium channels attenuates portal vein contractility induced by increased extracellular potassium concentrations [26].

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VO reviewed and analyzed the scientific literature, exposed the main postulates of the material entity, and approved the final version of the manuscript.

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