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IN VITRO MODELING AND VASCULAR PATHOPHYSIOLOGY OF INTRACRANIAL HEMORRHAGE

The effects of perivascular blood and β_1-receptor blocker nebivolol on vasomotor function of isolated cerebral arteries

Abstract of the Ph.D. thesis

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Abbreviations

4-AP	4-aminopyridine
5-HT	Serotonin
20-HETE	20-hidroxi-eikozatetraenoic-acid
AA	Arachidonic acid
AC	Adenylyl cyclase enzyme
BA	Basilar artery
BD	Basal Diameter
[BD%]	Normalized diameter in % of basal diameter
BK_{Ca}	Large conductance Ca^{2+}-activated potassium channel
BQ-485	Hexahydro-1H-azepinylcarbonyl-Leu-D-Trp-D-Trp-OH,-Na
BTXN	Butoxamine
CaM	Calmodulin
Ca-CaM	Ca^{2+}-calmodulin complex
CGRP	Calcitonin gene-related protein
COX	Cyclooxygenase enzyme
CSD	Cortical Spreading Depolarization
CSH	Cortical Spreading Hyperemia
CSI	Cortical Spreading Ischemia
E5555	1-(3-tert-butyl-4-methoxy-5-morpholinophenyl)-2-(5,6-diethoxy-7-fluoro-1-iminoisoindolin-2-yl)ethanone hydrobromide
EDTA	Ethylene-diamine-tetraacetic acid
eNOS	Endothelial nitric-oxide synthase enzyme
ER	Endoplasmic reticulum
$ET_{A/B}$	Endothelin-A/-B receptor
Fura2-AM	5-Oxazolecarboxylic acid, 2-(6-(bis(2-((acetyloxy)methoxy)-2-oxoethyl) amino)-5-(2-(2-(bis(2-((acetyloxy)methoxy)-2-oxoethyl)amino)-5-methylphenoxy)ethoxy)-2-benzofuranyl)-, (acetyloxy)methyl ester
H_1R	Histamine H_1-receptor
HB	Hemolyzed Blood
HET0016	N-hydroxy-N'-(4-n-butyl-2-methylphenyl)Formamidine
Hgb	Hemoglobin
HO-1/-2	Heme-oxygenase enzyme-1/-2
hRBC	Hemolyzed Red Blood Cell Concentrate
IBTX	Iberiotoxin
IK_{Ca}	Intermediate conductance Ca^{2+}-activated potassium channel
INDO	Indomethacin
$[K^+]$	Potassium-ion concentration
K_{ATP}	ATP-sensitive potassium channel
K_{Ca}	Ca^{2+}-activated potassium channel
K_V	Voltage-dependent potassium channel
KMUP-1	7-[2-[4-(2-Chlorophenyl)piperazin-1-yl]ethyl]-1,3-dimethylpurine-2,6-dione
L-Arg	L-Arginine
L-NAME	Nω-nitro-L-arginine-methyl-esther
MCA	Middle cerebral artery
MLCK	Myosin light chain kinase
NO	Nitric-oxide
ODQ	1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one
ozagrel	(2E)-3-[4-(1H-imidazol-1-ylmethyl)phenyl]acrylic acid
PBS	Phosphate-buffered saline
PD	Passive Diameter
[PD%]	Normalized diameter in % of passive diameter
PLTc	Intact platelet concentrate
PLTs	Decompartmentalized platelet suspension
PTA	Percutaneous transluminal (balloon) angioplasty
S1P	Sphingosine-1-phosphate
SAH	Subarachnoid hemorrhage
sGC	Soluble guanylate-cyclase enzyme
SK_{Ca}	Small conductance Ca^{2+}-activated potassium channel
SPPO	Stabile plasma protein solution
SQ22536	9-(Tetrahydro-2-furanyl)-9H-purin-6-amine
SQ29548	[1S-[1α,2α(Z),3α,4α]]-7-[3-[[2-[(phenylamino)carbonyl]hydrazino]methyl]-7-oxabicyclo [2.2.1] hept-2-yl]-5-heptenoic acid
TEA	Tetraethylammonium chloride
TP-receptor	Thromboxane-A_2/prostanoid receptor
VSM	Vascular Smooth Muscle

I. Part I: VASOMOTOR EFFECT OF PERIVASCULAR BLOOD ON ISOLATED CEREBRAL ARTERIES

I.1. Introduction

Regulation of the cerebral blood flow (CBF) is essential to supply the complex function of the brain, including nutrition of the brain tissue, optimal gas exchange between blood and interstitial space, and maintenance of intracranial pressure and volume at a constant level [1]. These processes, such as CBF are under complex, interdependent and heterogeneous regulation: cerebral autoregulation [1, 2], chemical (respiratory component) regulation [3, 4], neurogenic regulation [3, 5], metabolic regulation [3, 6-9], microvascular communication [9-15], and the neurovascular coupling [5, 16, 17].

The blood supply of the brain by the anatomical side comes from both the vertebro-basilar system (supplying the brain stem) and internal carotid artery branches (responsible for the blood supply mainly of the cerebrum) [18]. These two arterial systems are communicating through the circle of Willis situated on the base of the brain, which significance arises in case of pathological circulatory conditions, thus allowing the opportunity of equilibration and correction of intravascular pressure distribution. Cerebral arteries branches of pial arterioles, then penetrate through the Virchow-Robin space [19, 20] forming network of intraparenchymal arterioles, which then diverge to capillaries, thus creating cerebrovascular segments. Here capillaries are 6-7 μm in diameter, situated 40 μm in distance to each other, thereby creating ~ 650 km long network [21, 22]. Then the capillary network merges to the valve-less central/deep venules, then to superficial cortical veins, later forming sinuses (especially vulnerable to traumatic impact) on the surface, which then convey the blood into the jugular veins.

The effect of intracranial hemorrhage to the vasomotor function of cerebral vessels

Intracranial hemorrhage is a pathological condition that is associated with the interruption of the continuity of intracranial vessels and it may have traumatic or non-traumatic origin [23]. Traumatic intracranial hemorrhages should be classified as epidural, subdural, subarachnoid (SAH) and intracerebral depending on the relation to the meninges [23]. In the background of non-traumatic intracranial hemorrhage is usually cerebrovascular anomaly, which can be an extracerebral (e.g. subarachnoid) and intracerebral/parenchymal hemorrhage [24]. It has to be noted that stroke among developed countries is on the third place in mortality after cardiovascular disease and cancer, and is the most important factor of the serious, life-long disabilities [25]. In addition, while in western countries the mortality rate of traumatic brain injury ranges between 20-25%, in Hungary reaches 45% [26]. In case of craniocerebral traumas the incidence of SAH is outstanding [27-29], and the presence of SAH increases morbidity and mortality, as well [28, 29]. Furthermore, SAH is one of the major prognostic factor [27, 30], highlighting the importance of recognizing and clinical management of SAH.

Clinical and experimental studies showed that acute subarachnoid hemorrhage (SAH) due to traumatic brain injury [27-30] or stroke [31] is followed by serious local vasospasm [32], which can severely impair autoregulation [33-35] and reduce regional cerebral blood flow, thereby resulting in secondary ischemic brain injury [36-38] with the consequent loss of brain function. Based on previous studies, cerebral vasospasm may occur both 1) in acute (in 48 hours), and 2) in delayed phase (3-7 days later) of subarachnoid hemorrhage [39]. Early secondary ischemic brain injury after SAH is attributed - in part - by small vessel injury and parenchymal arterial dysfunction [40], vasoconstriction and consequential reduced cerebral blood flow thus determining the poor outcome after SAH [38, 39].

I.2. Hypotheses and aims of studies

Proper resistance (i.e. diameter) of cerebral arteries plays an important role in maintaining continuous blood supply of the brain to preserve its functions [2, 31, 41]. The perivascular blood can affect local tissues (neurons, glia cells, vascular cells, etc.), but primarily impairs the regulation of cerebrovascular tone endangering maintenance of normal flow to brain and thus functions [42-45]. Increased vascular contractility to perivascular blood may be attributed to endothelial dysfunction and/or increased contractility of vascular smooth muscle (VSM) [46]. However, during SAH-induced vasoconstriction, several mechanisms and multifactorial constrictor components [37, 46-72] can be involved in the pathological regulation of vascular resistance. Earlier experiments showed that purified hemoglobin induces vasoconstriction [49] of cerebral arteries, which was explained by its nitric oxide scavenging effect [47]. However, the vasoconstrictor effects of perivascular whole hemolyzed blood (HB), which is present in vivo during hemorrhage or traumatic brain injury have not yet been fully characterized [37].

We hypothesized that:

1.) HB and its components cause different degrees of cerebral vasoconstriction,
2.) perivascular HB reduces the diameter of the cerebral vessels via elevating $[Ca^{2+}]_i$ levels,
3.) in the development of vasoconstrictor effects of HB several proximal signaling pathways are activated, as well and its origin is multifactorial.

In order to test these hypotheses on cerebral vessels, we aimed to:

1.) characterize the vasoactive components of blood,
2.) clarify the underlying intracellular vasoconstrictor mechanisms using pharmacological agents with known mechanisms of action.

I.3. Materials and Methods

I.3.1. Animals

For these experiments ~2 months-old (250±50 g) male Wistar rats (Crl:WI, Charles River Hungary Kft; n=6-12 in each group) were used. Animals were housed on a 12h light/dark cycle and were ad-libitum fad on standard rat chow and free access to tap water. All experiments and interventions were undertaken according to the general rules and special approval of the University of Pecs Ethical Committee for the Protection of Animals in Research with the permission of County Government Office (BA 02/2000-8/2008, BA 02/2000-12/2011), in accordance with the directives of the National Ethical Council for Animal Research and those of the EU Directive (2010/63/EU), in accordance with the ARRIVE guidelines.

I.3.2. Isolation of cerebral arteries

Cerebral arteries were isolated as previously described [38, 73, 74]. In brief, animals were anesthetized by ether and decapitated according to Institutional Animal Care and Use Committee of University of Pecs, Medical School, Pecs, Hungary. The brains were immediately removed and placed in Krebs' buffer. Basilar arteries (BA) and middle cerebral arteries (MCA) were isolated from the brain of each animal. Segments of the BAs and MCAs were isolated using microsurgery instruments.

I.3.3. Functional measurements in vessel chamber

Both ends of the arteries were mounted onto two glass micropipettes in a vessel chamber and pressurized to 80 mmHg with zero flow. The diameters of micropipettes were matched in order to prevent pressure- and flow-disturbances due to different hydrodynamic resistance. Inner vascular diameter was measured with a video-micrometer system and continuously recorded using a computerized data acquisition system (LabChart 7 pro by PowerLab, ADInstruments, Australia). All arteries were allowed to stabilize for 60 min in oxygenated (21% O2; 5% CO2; 74% N2) Krebs' buffer (at 37°C). After the equilibration period, during which spontaneous myogenic tone developed (measured as a basal diameter; BD), and the vascular responses were assessed, as reported previously [38, 73, 74]. At the end of each experiment the passive diameters (PD) of the vessels were measured at 80 mmHg intraluminal pressure in the presence of Ca^{2+}-free Krebs' buffer containing the L-type Ca^{2+}-channel inhibitor nifedipine (10^{-4} mol/L) to achieve maximal vasodilatation. Significant difference between BD and PD indicated the integrity of contractile elements during measurements, and the validity of functional vascular responses under specific experimental conditions. If the BD and PD did not differ significantly, we have not performed any experiment on that vessel.

I.3.4. Administration of Vasoactive Agents and Inhibitors

Intact endothelial function, was tested by vascular responses to acetylcholine (ACh) and adenozin triphosphate (ATP) [75], whereas that of smooth muscle by sodium nitroprusside (SNP), ATP and the L-type Ca^{2+} channel inhibitor nifedipine, which was also used to assess the passive diameter (PD) of arteries. To assess the vasodilator effect of elevated carbon dioxide (CO_2), 15% CO_2; 21% O_2; 64% N_2 gas mixture were used to bubble Krebs' buffer (for 5 minutes; at 37°C) in vessel chamber, as previously reported [38]. For testing the receptor-independent vasoconstriction 10-60 mmol/L KCl was used [76].

The vasomotor effect of perivascular blood was investigated by adding autologous hemolyzed whole blood (HB) directly into the vessel chamber. Hemolyzed whole blood (200 µL) was prepared by osmolysis from 40 µL whole blood (B) and 160 µL bidestillated water (DW) at ratio B:DW=1:4. In other series of experiments vasomotor function of cerebral arteries were studied in response to blood components, such as blood serum (20 µl), blood plasma (20 µl), hemolyzed red blood cell (hRBC; 20 µl), intact platelet concentrate (PLTc; 10 µl), decompartmentalized platelet suspension by osmolysis (PLTs; 100 µl) and purified hemoglobin (Hgb).

We have investigated the role of prostanoids in the development of HB-induced vasoconstriction. Thus the synthesis of prostanoids was inhibited by non-selective COX inhibitor indomethacin [77] (INDO; $5x10^{-5}$ M, 30 min; n=11), which was tested by arachidonic acid [78, 79] (AA, 10^{-5} M, 15 min; n=11). The effect of thromboxanes was tested by TP-receptor (TXA_2/PGH_2-receptor) antagonist [1, 77] (SQ29548; 10^{-4} M; 20 min; n=7). During the characterization of SQ29548, TP-receptor agonist, a synthetic PGH_2 analogue [79, 80] (U46619; 10^{-7} M, n=9) was used on BA. Endothelial NO synthase was blocked by L-NAME [81] (10^{-4} M; 20 min; n=5-11). All drugs were purchased from Sigma Aldrich (Budapest, Hungary), except HET0016 and SQ29548, which was purchased from Cayman Chemicals (Cayman Europe, Tallinn, Estonia). Potassium concentration was measured by Nova Biomedical pHOx plus blood gas analyzer (Massachusetts, USA).

I.3.5. Assessment of intravascular calcium ion level

As described previously [82] changes in intracellular Ca^{2+}-ion concentration were assessed with ratiometric (R) calcium-measurement at the wavelength of 340 nm and 380 nm using Fura2-AM fluorescent dyes [83, 84]. The physiological Krebs' solution was supplemented with Fura2-AM (5 µmol/L) fluorescent Ca^{2+} indicator dye and BSA (bovine serum albumin; 1%) for 60 min during which spontaneous myogenic tone developed. We have used fluorescent microscope to measure intravascular Ca^{2+} concentrations by an IncyteIm2 instrument (Intracellular Imaging Inc, Cincinnati, OH, USA) by recording images (cut off >510 nm) excited alternatively by 340 and 380 nm wavelengths. Images were recorded every 4 s and evaluated offline. Arterial Ca^{2+} concentrations were detected

by calculating ratios (R) between averaged signal intensity at 340 and 380 nm excitation in the whole arterial segment.

I.3.6. Statistical Analysis

Experimental results are presented as mean ± S.E.M. Data are expressed as either micrometer or percentage of basal [BD%] and passive diameter [PD%]. The changes in ratiometric intracellular calcium measurements are indicated either as ratio (R) or as a delta ratio (ΔR). Statistical analysis was performed after normality-test by one-way ANOVA (Holm-Sidak method) or Student's t-test as appropriate by SPSS 11.0 for Windows software. P-values <0.05 were considered to be statistically significant. Figures were made by SigmaPlot 11.0 for Windows.

I.4. Results

I.4.1.1. Vasomotor effect of hemolyzed blood (HB) on cerebral arteries

HB elicited significant constrictions of BA and also in MCA, while after wash-out of HB the basal diameters of cerebral arteries reached the control level.

I.4.1.2. Changes in agonist-induced vasomotor responses to HB

ACh and **SNP** induced vasodilation both in BA and MCA, while during the administration of HB and after the wash-out dilations were significantly reduced.

Nifedipine and **CO_2** induced vasodilation in cerebral arteries, while neither in the presence nor after wash-out dilations were decreased in BA and MCA.

Exposure of **CO_2** significantly increased pCO_2 of a Krebs' buffer, while significantly decreased pH. CO_2 significantly increased the basal diameter and it restored the basal diameter in the presence of HB, as well.

Dilator effect of **nifedipine** did not differ from a **nimodipine**, a high specific cerebrovascular Ca^{2+}-channel inhibitor, commonly used in SAH therapy.

I.4.1.3. Vasomotor effect of components of HB on BA

$[K^+]$ concentration of Ca-Krebs' buffer significantly increased in the 0. minute of the administration of HB. 20 mM KCl caused significant dilation, while 60 mM KCl caused significant constriction as an extent of HB.

A synthetic PGH_2 analogue U46619 caused significant vasoconstriction on BA, which was significantly inhibited by TP-receptor (TXA_2/PGH_2-receptor) antagonist SQ29548.

HB, SQ29548+HB and indomethacin+HB caused significant vasoconstriction at a same rate on BA.

Administration of arachidonic acid (AA) induced biphasic vasomotor effect, first caused significant constriction then significant dilation in BA. After the incubation with indomethacin both the constriction and dilation was significantly reduced.

I.4.2. Vasomotor effect of blood serum on BA

Autologous serum induced significant vasoconstriction on BA, while wash-out of serum caused significant dilation, thus basal diameters reached the control level.

The ACh, SNP and nifedipine induced significant vasodilation on BA. In the presence of serum the ACh- and SNP-induced dilation decreased but the nifedipine-induced dilation remained intact. After wash-out of serum the ACh-induced dilation was decreased, but neither SNP-, nor nifedipine-induced dilation has changed.

I.4.3. Vasomotor effect of hemolyzed Red Blood Cell Concentrate (hRBC) on BA

Autologous hRBC induced significant vasoconstriction on BA, while wash-out of hRBC caused significant dilation, thus basal diameters reached the control level.

The ACh, SNP and nifedipine induced significant vasodilation on BA. In the presence of hRBC or after wash-out while the ACh- and SNP-induced dilation decreased, the nifedipine-induced dilation remained intact.

I.4.4. Vasomotor effect of blood plasma on BA

Autologous blood plasma (plasma) induced significant vasoconstriction on BA, while wash-out of plasma caused significant dilation, thus basal diameters reached the control level.

The ACh, SNP and nifedipine induced significant vasodilation on BA. While in the presence and wash-out of plasma neither the ACh- nor the nifedipine-induced dilation has decreased, but SNP-induced dilation has decreased.

I.4.5. Vasomotor effect of platelets on BA

Intact platelet concentrate (PLTc) did not cause significant vasoconstriction, while decompartmentalized platelet suspension (PLTs) induced significant vasoconstriction and after wash-out caused significant dilation, thus basal diameters reached the control level of BA.

I.4.6. Vasomotor effect of hemoglobin on BA

Purified hemoglobin (Hgb) did not cause vasoconstriction (10^{-12} M - 10^{-6} M) on BA, and after wash-out of Hgb the basal diameter has not changed. The HB-induced significant vasoconstriction did not differ from L-NAME+HB induced significant vasoconstriction.

I.4.7. Changes in vascular $[Ca^{2+}]_i$ in response to HB on BA

Perivascular HB elicited increases in ratiometric (R) Ca^{2+}-signal in a concentration-dependent manner, indicating increase in intravascular $[Ca^{2+}]_i$ concentrations. After wash-out the ratio significantly decreased resulting in dilation.

I.4.8. Vasomotor effect of perivascular blood and its components on BA

The HB, serum, hRBC, plasma, PLTs elicited significant vasoconstriction on BA, while neither PLTc nor Hgb caused vasoconstriction. Significant difference has been appeared in the extent of vasoconstriction between HB and serum, serum and hRBC, then hRBC and plasma. There wasn't difference between plasma and PLTs, but could be observed difference between PLTs and PLTc. We have not found difference between PLTc and Hgb.

I.5. Discussion of findings

I.5.1. Hemolyzed blood elicits vasoconstriction both in basilar and middle cerebral arteries

In all experiments vessels developed myogenic tone [1, 2, 85, 86] (passive diameters vs. basal diameters), thus vasomotor capacity of both basilar (BA) and middle cerebral arteries (MCA) could be observed in the presence of optimal tone, without the use of pre-constrictor, which could interfere with cellular vasomotor mechanisms. The data show that addition of HB to the chamber caused significant constrictions in basilar arteries. Interestingly, after washout of HB, basal diameter returned to the control level. Importantly smaller intracerebral arteries (middle cerebral artery) are also responded with constriction to HB. It is likely that even smaller arterial vessels are affected by HB as previous studies showed that myogenic tone of pial vessels were impaired even after washout of blood [59]. Nevertheless, HB may elicit vasomotor responses, which are region-specific.

I.5.2. Potential mechanisms of reversal of HB-induced constrictions

Interestingly, data reported in the literature regarding the effect and mediation of $\mathbf{CO_2}$-induced dilations of cerebral vessels are not unequivocal. For example, the nature of response (dilation or constriction) varied depending on the experimental conditions. The potential effect of changes in pH was supported by some [87, 88], but refuted by other studies [89-91]. There were studies suggesting endothelial [87, 92] and nitric oxide mediations [88], and role for arachidonic acid metabolites [92, 93], SK_{Ca}/IK_{Ca} channels [92, 94] and also changes in vascular cell membrane polarization [95, 96]. Because of the aforementioned we felt it is important to establish the effects of pCO_2 on the vasomotor tone of isolated cerebral arteries, especially in the presence of HB; a condition in which the presence of in vivo confounding factors can be excluded. CO_2 significantly increased pCO_2 and decreased pH of vessel-chamber. CO_2 elicited significant vasodilation even in the presence of HB, thereby restoring the basal diameter.

Several clinical studies proved the dilator effect of **nimodipin**, which is highly specific for cerebral vasculature [97-101]. **Nifedipine**-induced dilation [38, 73] did not differ from the nimodipin-induced dilation, and dilations of BA and MCA was not affected by HB, or wash-out.

Previous studies raised the importance of removal of blood from the extravascular space [102, 103]. Based on our data **washing out of HB** basal diameter returned to control level both in BA and MCA, emerging the importance of evacuation of perivascular blood. Despite the return of the basal diameter to control, HB impairs endothel- and smooth muscle-dependent, NO-mediated vasodilation, as supported by others [37, 49, 104-106].

The finding that vasoconstrictor effect of HB can be reversed by wash-out of blood or decreasing intracellular Ca^{2+} concentration using locally applied Ca^{2+}-channel antagonists, or increasing locally perivascular pCO_2 suggest a key role for intracellular Ca^{2+} level rather than to calcium sensitivity. Also, it seems that high pCO_2 and nifedipine is powerful enough to overcome any constrictor mechanisms or factors operating during hemolysis of blood. We believe that extrapolating these experimental findings to clinical conditions may open up novel therapeutic avenues for subarachnoid hemorrhage especially the powerful effect of perivascular application of high pCO_2 should be explored and documented.

I.5.3. Potential mechanisms of perivascular blood and its components-induced constrictions

As we mentioned before, **blood** contains myriad of vasoactive components [37, 46-72], thereby may have a complex role in the mechanisms of blood-components-induced vasoconstriction, thus future studies need to single out the mechanisms finally leading to constriction.

Serum via activating coagulation cascade may contain eicosanoids [52] / prostanoids [53, 107]. However, considering results of our experiments, neither non-selective COX-inhibitor indomethacin, nor TXA_2/PGH_2 receptor blocker SQ29548 inhibited significantly the HB-induced vasoconstriction. According to the others [61, 63] neither derivates of arachidonic acid (AA) nor TXA_2/PGH_2 receptors seems to play role in the development of HB-induced vasoconstriction. Furthermore, serum may contain other, a CYP450 derivate 20-HETE [51, 52], low molecule weight peptides (e.g. endothelin-1 [9, 66, 108, 109]), or thrombin [46, 55, 65, 67, 110], which may cause vasoconstriction. We have tested indomethacin as a COX-inhibitor using AA. AA induced biphasic vascular response on cerebral arteries: first constriction, than dilation, which was significantly reduced using indomethacin.

Plasma circulating with inactive coagulation factors has significantly less vasomotor activity than serum, but containing fibrinogen [68, 70, 111] or plasma proteins [56, 58] may result in vasoconstriction.

Hemolyzed red blood cell concentrate (hRBC) elicited significant vasoconstriction, which could be explained – in part – by released hemoglobin and bilirubin oxidation products (BOX) [47, 49] and elevated $[K^+]$

level [37, 50, 59] derived from decompartmentalized RBC. Based on our experiments the $[K^+]$ concentration has significantly increased in the presence of HB and the KCl caused significant constriction, as well. Furthermore, $[K^+]$ may be released from both RBC and whole blood during the hemolysis, thus raising the possibility that $[K^+]$ has a putative role of in the development of perivascular blood-induced vasoconstriction.

Interestingly, previous studies showed, that **hemoglobin and its metabolites, the bilirubin oxidation products (BOX)** [47, 49, 59, 112, 113] induces vasoconstriction, however our experimental data could not confirm. It is possible, that the hemoglobin do not take a significant part in the development of HB-induced vasoconstriction. To support these data, we have shown that HB elicited vasoconstriction even if blocking the eNOS using L-NAME, thus modeling the constrictor mechanism via Hgb-NO interaction.

Interestingly, while the **platelet concentrate** did not induce, but **platelet suspension** (decompartmentalized by osmolysis) elicited significant vasoconstriction in cerebral arteries, probably by the release of high concentration in platelet-derived vasoactive agents. While previous studies showed the role of TXA_2 in cerebral circulation [54, 114] and in SAH [62], we could not prove this by inhibiting TP-receptors, as others reported [61, 63, 115]. The discrepancy could be solved because the role of TXA_2 could have been reduced in the multifactorial, HB-induced vasoconstriction, and/or TXA_2 is not released, indeed. Furthermore, a high concentration of platelet-derived vasoactive agents (serotonin [51], histamine [60, 103], sphingosine-1-phosphate [64, 116-118]) may be released after decompartmentalization of platelets thereby causing substantial constriction.

Based on the inhibition and impairment of HB-induced, endothel- and smooth muscle-dependent, NO-mediated mechanisms, we can speculate that HB (and KCl) directly affects the function of SMC, causing depolarization [89] and consequent Ca^{2+}-release, via elevation of $[K^+]$ level.

In the effect of **Cortical Spreading Depolarization (CSD)** [119] can participate several vasoactive molecules released during SAH, like elevation of the $[K^+]$, the oxyhemoglobin, decreased biological availability of NO, elevated glutamate-level, and increased expression of ET-1 [120, 121]. In the background can be identified vasospasm of large arteries following SAH, then compensatory vasodilation of small pial arteries in the early phase of spasm (Cortical Spreading Hyperemia, CSH). In the acme phase of vasospasm CSD occurs as a result of aforementioned vasoconstrictor mechanisms that results in reduced regional CBF thereby evolving the consequential Cortical Spreading Ischemia (CSI) and delayed cerebral vasospasm [46] (**Fig 1.**).

I.5.4. Effect of HB and its components on agonists-induced dilations of cerebral arteries

Many previous studies [2, 122, 123] established that endothelium-derived factors are important in the modulation of vasomotor tone of cerebral arteries. Previous data showed that oxyhemoglobin induces significant constriction of cerebral arteries which was explained – in part - by binding nitric oxide (NO) [47, 49]. On the other hand hemoglobin may act directly on smooth muscle cell by activating tyrosine-kinase thus inactivating voltage dependent potassium channels ($K_V1,5$) [59]. Furthermore it has been published reduction in the $K_v2,2$ channel expression in canine SAH model [124].

Our data show that in the presence and after washout of **HB**, ACh- and SNP-induced dilations were significantly reduced [69], suggesting that HB affects both endothelial- an smooth muscle-dependent, NO-related mediations, which remained impaired even after washout of HB, as others reported [37, 49, 104-106, 125]. These findings suggest that although HB-induced constrictions can be reversed, some of the important vasomotor mechanisms remain impaired, which may have clinical significance. Neither Ca^{2+}-channel antagonist nor CO_2-induced vasodilation was affected by HB, and the extent of dilation did not differ from each other, suggesting that CO_2 probably may act via hyperpolarisation [92, 94] and may have Ca^{2+}-antagonist properties [95, 96].

Serum impairs the endothel-dependent dilator mechanisms even after wash-out. Interestingly, while in the presence of serum the VSM-dependent mechanisms were inhibited, after wash-out we have not detected decrease in dilation. It raises the possibility that constrictor agents of serum are mainly associated to endothelium, while the inhibition of VSM was only transient. The nifedipine-induced dilation was affected by neither the presence nor the wash-out of serum.

In the presence and after wash-out of **hemolyzed RBC** vasodilation significantly decreased due to impairment of endothel- and VSM-dependent mechanisms. Our data suggest that in the effect of hRBC-induced vasoconstriction, thus in the prolonged inhibition of dilation probably may play part the release of bilirubin oxidation products [47], and the elevated K^+-level, as others reported [37, 50, 59] (Part I.5.3). Hemolyzed RBC and the wash-out did not affect the Ca^{2+} -channel inhibitor-induced vasodilation.

Interestingly, regarding to administrations of **plasma** the endothel-dependent vasodilation were not, while VSM-dependent dilations were impaired even after wash-out. Based on previous studies, in the background of the effect of plasma in the inhibition of dilation several components can be identified, including fibrinogen [68, 70, 111] and other plasma proteins [56, 58]. This can be explained by impairment of primarily the VSM-mediated dilatory mechanisms due to its high molecular weight, administered from the extravascular space. Plasma and the wash-out did not affect the nifedipine-induced vasodilation.

Based on aforementioned reasons the endothel- and VSM-dependent dilator mechanisms were impaired, while the CO_2- and the Ca^{2+}-channel inhibitor nifedipine-induced dilations remained intact either exposure of HB and its components, or after wash-out.

To sum it up, despite the inhibition of endothel- and VSM-dependent dilator mechanisms, blood and its components-induced vasospasm could be reversed by CO_2, Ca^{2+}-channel blockers and wash-out, thereby restoring basal diameter of cerebral arteries, thus highlighting the importance of therapeutical consequences and serving basis of further studies.

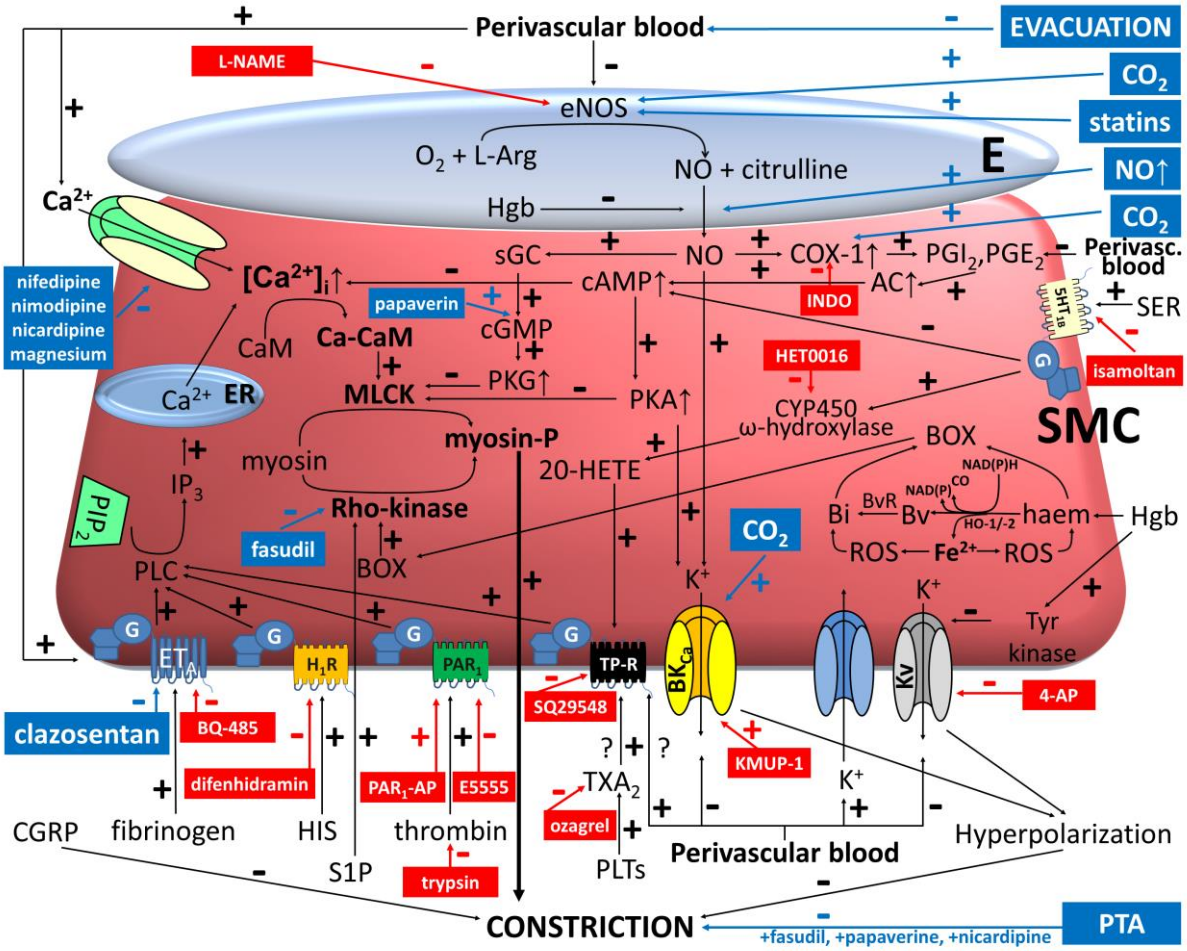

Fig 1. Proposed mechanisms of vasomotor effect of perivascular blood and its components on cerebral vessels (black arrows), and suitable agents for experimental testing of abovementioned mechanisms (red arrows), and potential therapeutic targets in the development of perivascular blood- and its components-induced vasoconstriction (blue arrows).

Explanation see in previous text (Part I.1.2.2, I.1.2.3, I.1.2.4. and part I.5.). Abbreviations used in Fig 1: + activates; - inhibits; E: endothelium; SMC: vascular smooth muscle cell; L-Arg: L-Arginine; NO: nitric oxide; sGC: soluble guanylate-cyclase; cGMP: cyclic guanosine monophosphate; PKG: proteinkinase-G; MLCK: myosin light-chain kinase; COX-1: cyclooxygenase-1; PGI_2/PGE_2: Prostaglandine I_2/E_2; AC: adenylyl cyclase; cAMP: cyclic adenosine monophosphate; PKA: proteinkinase-A; PIP_2: phosphatidil-inositol-biphosphate; PLC: phospholipase-C; IP_3: inositol triphosphate; ER: endoplasmic reticulum; CaM: calmodulin; Ca-CaM: Ca^{2+}-calmodulin complex; ET_A: endothelin-A receptor; BQ-485: enothelin-A receptor antagonist; H_1R: histamine H_1 receptor; HIS: histamine; PAR_1: protease activated receptor-1; PAR_1-AP: PAR_1 activating peptide; E5555: PAR_1 antagonist; TP-R: TXA_2/PGH_2 receptor; SQ29548: TP-R antagonist; ozagrel: TXA_2 synthesis inhibitor; PLTs: decompartmentalized platelet suspension; BK_{Ca}: large conductance Ca^{2+}-activated K^+-channel; KMUP-1: nonselective BK_{Ca} channel inhibitor; Kv: voltage-dependent K^+- channel; 4-AP: 4-aminopiridine, Kv channel inhibitor; Hgb: hemoglobin; Tyr-kinase: tyrosine-kinase; ROS: reactive oxygen species; BOX: bilirubin oxidation products; CO: carbon-monoxide; HO-1/-2: heme oxygenase-1/-2; Bv: biliverdin, BvR: biliverdin reductase; Bi: bilirubin; SER: serotonine; $5HT_{1B}$: serotonine $5HT_{1B}$ receptor; INDO: indomethacin, nonselective COX inhibitor; HET0016: CYP450 ω-hydroxylase inhibitor; 20-HETE: 20-hydroxy-eicosatetraenoic-acid; PTA: percutan transluminal angioplasty; CO_2: carbon-dioxide; CGRP: calcitonin gene-related peptide; L-NAME: Nω-nitro-L-arginine-methyl-esther; S1P: sphingosine-1-phosphate.
Non-marked pathways: PAR_1 receptor and the S1P decreases the activity of AC via G_i-mediated pathway, thereby eliciting indirect vasoconstriction.

I.5.5. Hemolyzed blood increases the level of vascular wall $[Ca^{2+}]_i$

HB, in a concentration-dependent manner increased the ratiometric (R) Ca^{2+} signal indicating increase in intravascular $[Ca^{2+}]_i$ concentration [82-84]. Since we have found that HB elicited constrictions of basilar arteries, we hypothesized that regardless of proximal signaling pathways, HB by increasing the intravascular Ca^{2+} level, results in constrictions. Interestingly, wash-out of HB, significantly decreased the $[Ca^{2+}]_i$ reaching the control level. The findings regarding the parallel changes in the vascular $[Ca^{2+}]_i$ and the diameter suggests that the final signaling mechanism by which HB elicits constriction of cerebral arteries is an elevation of smooth muscle intracellular Ca^{2+} concentration but not the Ca^{2+}-sensitivity. Our results were supported by some [59, 126], but refuted by others [46].

I.5.6. Clinical implications

Searching for effective pharmaceutical treatments to improve cerebral blood flow in diseased conditions, such as hemorrhagic stroke [33, 127] and or traumatic brain injury (TBI) [27-30, 35] is an ongoing clinical effort. In these conditions the resistance of cerebral vessel greatly increases reducing the regional blood supply of brain and impairs parenchymal arterial functions [35, 40]. We believe that extrapolating these experimental findings to clinical area, may open up novel therapeutic possibilities for the subarachnoid hemorrhage and traumatic brain injury, thereby creating an opportunity in optimization of impaired cerebral circulation.

Direct perivascular application of HB (without traumatic brain injury, and in the absence of neural or other tissue factors) elicited substantial constrictions of cerebral arteries, via elevating vascular $[Ca^{2+}]_i$ level, which however can be reversed by local application of calcium channel antagonist or high pCO_2 or wash-out of blood.

I.6. Summary of novel findings of Part I

1. Perivascular hemolyzed blood elicits significant and substantial constriction of basilar and middle cerebral cerebral arteries.
2. These functional vasomotor responses correlates with changes in vascular Ca^{2+}-signal
3. Vasoconstrictor effect of perivascular blood and its components could be reversed by calcium antagonist nifedipine, increasing CO_2 level or wash-out of blood
4. Perivascular hemolyzed whole blood and its components severely impaired the endothel- and smooth muscle-dependent, NO-mediated dilator mechanisms on cerebral arteries, that remained impaired even after wash-out of blood.
5. Perivascular hemolyzed whole blood, serum, hemolyzed red blood cell concentrate, plasma and decompartmentalized platelets has a significant and substantial role in the development of vasoconstriction.

II. Part II: VASOMOTOR EFFECT OF NEBIVOLOL ON ISOLATED CEREBRAL ARTERIES

II.1. Introduction

Many cerebral diseases (hypertensive encephalopathy, vascular cognitive impairment, Alzheimer's disease, traumatic brain injury or stroke) are associated with impaired regulation of cerebral blood flow. [2]. Thus experimental and clinical investigations aim to improve regulation of cerebral blood flow by pharmacological means [128]. In addition to the improvement of the modulatory role of endothelium (for example via nitric oxide (NO) [129-132], the restoration of the appropriate regulation of smooth muscle tone of cerebral vessels is also of great importance [132, 133].

One of the most frequently used therapeutic agents modulating the regulation of cardiovascular system are the **β-adrenergic receptor blockers** (β-blockers). β-blockers has become to a leading position in pharmacotherapy of heart failure and hypertension in the last third of last century [134]. Nowadays, it is recommended as a front-line agent in monotherapy of hypertension (evidence II/B-ESH/ESC 2013) [135], in hypertension and concomitant chronic obstructive pulmonary disease (COPD) (ESH/NEWS-N51 IIB) [136-138], as dual combination therapy of hypertension and heart failure (evidence I/A-ESH/ESC 2013) [138], as triple combination therapy in ischemic heart disease/coronary artery disease [139], in heart failure [140], or in case of tachycardias [141] (evidence I/A-ESH/ESC 2013) [138]. There are several differences between generations of β-blockers, including β_1-selectivity, membrane stabilizing effect, intrinsic sympathomimetic activity (ISA) and vasodilator effect [134].

Nebivolol is a 3rd generation β_1-blocker [142, 143]. It is a mixture of the 2 enantiomers, D-nebivolol (+SRRR) and L-nebivolol (-RSSS) and is highly specific for β_1 receptors [143-145]. Regarding the high residual peak effect (90%), it is sufficient to use once daily, and the suspension does not involve rebound effect as other β-blockers [134]. Nebivolol can effectively reduce both the peripheral and central blood pressure, in which the latter positive effect excels among other β-blockers [136], and compared to atenolol, nebivolol significantly greater decreased the aortic pulse pressure [146].

Based on clinical studies, nebivolol is particularly advantageous in **heart failure**, since decreases heart rate, decreases pre- and afterload, the left ventricular end-diastolic pressure and increases stroke volume [134]. The ENECA study showed that the left ventricular ejection fraction and quality of life has improved (>65 years old) [147]. In SENIORS study in case of heart failure patients (<35% EF; >70 years old) total mortality decreased by 38% [148].

Previous studies have shown that nebivolol has **beneficial metabolic profile**, since it does not modify negatively either carbohydrate or lipid metabolism [149-151]. Nebivolol did not cause weight gain, and did not increase the frequency of new onset of diabetes [148]. According to Celik et al. nebivolol increased insulin sensitivity and decreased insulin resistance [152], others have also shown that insulin sensitivity were not reduced [151, 153, 154]. According to Celik's and Lacourciere's groups nebivolol decreased LDL- and total cholesterol levels [152, 155], Makolkin et al. reported decrease in serum triglyceride levels [156].

In patients with **COPD**, the use of β-blockers has been contraindicated for long time, however, the appearance of nebivolol has now became applicable in case of coexistence of other indications (ESH/NEWS-N51 IIB) [138]. Numerous studies have shown the safety of use of nebivolol in COPD patients [157, 158], since it does not impair the functional respiratory parameters [159, 160], and it reduced the mortality [161]. In vitro studies [162] and clinical investigations have confirmed that nebivolol reduces oxidative stress and the concentration of soluble P-selectin, and increases the adiponectin concentration [152], that may play an important role in inhibiting of the inflammation of airways in COPD patients [138].

Nebivolol **did not cause erectile dysfunction**, also the increase in sexual activity has been described in comparison with other β-blockers [163]. Nebivolol did not influenced physical activity [149], and unlike most of the β-blocker, it did not cause sleep disorders, also significantly improved the quality of life of patients [164].

As previously described, nebivolol possesses **vasodilator** properties [143, 148], and may have a significant effect in **NO-mediated pathway** in various tissues and organs [165], and reduces the inactivation of NO, decreases the level of ADMA (eNOS inhibitor) [162], furthermore increases the activity of eNOS [166]. Previous work by Ignarro et al. [167] found that nebivolol elicits relaxation of canine coronary and pulmonary artery by stimulating endothelial NO synthesis, which may have a role in the development of antihypertensive effect [168]. Supporting this conclusion, Gao et al. [169] showed that nebivolol elicits endothelium-dependent relaxation in canine coronary rings, whereas further studies also showed its dilator effects on human forearm veins and arteries [170, 171]. Interestingly, Ignarro et al. showed both endothelium-dependent and -independent relaxations in rat aortic rings [167]. However, it is important to note, that nebivolol elicited vasorelaxation even in case of inhibited eNOS, which may be attributed to endothelial hyperpolarizing factor [167]. Considering above mentioned, this dual effect may be critically important in case of decreased NOS activity and/or associated with decreased NO bioavailability, such as in ischemic conditions [172-174].

Interestingly, some studies have been reported that **other β-blockers** induced vasorelaxation in both central and peripheral arteries [175-177]. Sakanashi et al. reported propranolol-induced relaxation in canine coronary arteries, and described the effect of the reduction of Ca^{2+}-influx [177]. Priviero et al. proved on rat aortic and mesenteric arteries that in the development of propranolol-induced relaxation may play part the effect of the reduction of Ca^{2+}-influx, independently of the inhibition of β-adrenergic receptors [176]. Cekic et al. showed that the β-blocker propranolol may have Ca^{2+}-antagonist effect in rat basilar artery [175].

Subarachnoid hemorrhage (SAH) due to traumatic brain injury [27-30] or stroke [31] is followed by serious local vasospasm [32], which can severely impair autoregulation [33-35] and reduce regional cerebral blood flow, thereby resulting in secondary ischemic brain injury [36-38] with the consequent loss of brain function, furthermore, significantly increases the morbidity and mortality of SAH [27-30]. Previously, we have shown that perivascular hemolyzed blood elicits significant constrictions of basilar arteries [38]. The importance of the study is justified with the still limited availability of therapeutic means - without major side effects - to improve cerebral blood flow supply in diseased conditions.

II.2. Hypotheses and aims of studies

As of today, there are no data regarding the direct effect of nebivolol on cerebral arteries without the potential brain tissues-derived confounding factors. Thus in this study we hypothesized that nebivolol:

1.) increases diameter of cerebral arteries via several intracellular mechanisms,
2.) primarily via NO-mediated signaling pathway presumed from the literature, and
3.) via decreasing vascular $[Ca^{2+}]_i$, and
4.) may restore the perivascular hemolyzed blood-induced vasoconstriction.

To test the hypothesis we aimed to:

1.) characterize vasomotor effect of nebivolol on isolated rat cerebral arteries, in control conditions, without the potential brain confounding factors.
2.) clarify intracellular vasodilator mechanisms using inhibitors of known mechanisms of action.

Regarding the anatomical position of basilar artery, it has important and special functional role in blood supply of brainstem [178] and circle of Willis, thus we have used isolated basilar arteries in our experiments.

II.3. Materials and Methods

II.3.1. Animals

As previously described (Part I.3.1.) for these experiments we have used basilar arteries (BA) isolated from ~2 months-old (250±50 g) male Wistar rats. The breeding and rearing of animals were the same as reported previously (Part I.3.1.).

II.3.2. Isolation of cerebral arteries

Cerebral arteries were isolated as we previously reported [38, 73, 74], described in detail in Part I.3.2.

II.3.3. Functional measurements in vessel chamber

Isolated cerebral arteries were mounted onto two glass micropipettes in a vessel chamber of 5 ml and pressurized to 80 mmHg with zero flow. Inner vascular diameter was measured with a video-micrometer system and continuously recorded using a computerized data acquisition system. Further investigations of vasomotor responses of BA were performed as previously described in Part I.3.3.

II.3.4. Assessment of endothelial function

To evaluate the role of endothelium in the development of nebivolol-induced dilation, the vascular endothelium was removed, as described previously [74]. The function of arteriolar endothelium and smooth muscle was assessed before and after endothel-denudation. Arteriolar dilations to a test dose of endothelium-dependent acetylcholine (ACh) and endothelium-independent sodium nitroprusside (SNP) were obtained. The endothelium was denuded by perfusing the vessel with 2 ml air (2 x [1 ml air in 5 minutes]), then filled and reperfused with Krebs' buffer thus cleaning debris. Vessels achieved a steady-state diameter in ~15 minutes, whereupon responses to ACh and SNP were retested.

II.3.5. Administration of vasoactive agents and inhibitors

In the first series of experiments vasomotor function of vessels was studied in response to increased concentrations (10^{-7} M to 10^{-4} M) of nebivolol. To assess endothelial function, vascular responses to acetylcholine (Ach) and adenosine-triphosphate (ATP) [75] were obtained. The intact vasomotor function of smooth muscle was verified by dilation to sodium nitroprusside (SNP) and ATP. In separate experimental series to assess the role of nitric oxide, endothelium-mediated responses were reassessed in the presence of NO synthase inhibitor L-NAME [81]. In other experiments soluble guanylate cyclase was blocked by ODQ [179]. To assess the efficacy of ODQ, ACh- and SNP-induced responses were obtained before and after incubation of vessels with ODQ. In other experimental series adenylyl cyclase was blocked by SQ22536 [180, 181]. In separate series of experiments to assess the role of β_1 adrenoceptors in the development of nebivolol-induced dilation, we have used β_1 adrenoceptor antagonist atenolol. In other experiments to investigate the role of β_2 specific adrenoceptors in the development of nebivolol-induced dilation, β_2 specific adrenoceptor antagonist butoxamine [182, 183] was used (BTXN). To assess the function of Ca^{2+}-activated potassium channels in the development of nebivolol-induced dilation, Ca^{2+}-activated potassium channel were blocked by TEA [182, 183] or large conductance Ca^{2+}-activated potassium channels were blocked by iberiotoxin [182, 183] (IBTX). Other experimental series tested the effect of nebivolol on BA in the presence of denuded endothelium or specific blockers separately LNAME, ODQ, SQ22536, BTXN, atenolol, TEA or IBTX, respectively. In separate series of experiment the vasomotor effect of perivascular blood was investigated by adding autologous hemolyzed blood (HB) directly into the vessel chamber. Hemolyzed blood (200 µL) was prepared by osmolysis from 40 µL whole blood (B) and 160 µL bidestillated water (DW) at ratio B:DW=1:4, as previously described [38]. At the end of each experiment the passive diameters of the vessels were measured at 80 mmHg intraluminal pressure in the presence of Ca^{2+}-free Krebs' buffer containing the L-type Ca^{2+} channel inhibitor nifedipine to achieve maximal vasodilatation. All drugs were purchased from Sigma Aldrich, except ODQ, SQ22536 and iberiotoxin (Cayman Europe). Nebivolol was provided as gift by Berlin-Chemie/A. Menarini Ltd.

II.3.6. Assessment of vascular smooth muscle calcium ion level

As described previously [38, 82, 184] in part I.3.5., changes in intracellular Ca^{2+}-ion concentration were assessed with ratiometric (R) calcium-measurement at the wavelength of 340 nm and 380 nm using Fura2-AM fluorescent dyes [83, 84]. During the incubation period of cannulated and pressurized artery the physiological Krebs' solution was supplemented with Fura2-AM (5 µM) fluorescent Ca^{2+} indicator dye and BSA (bovine serum albumin; 1%) for 60 min during which spontaneous myogenic tone developed. We have used fluorescent microscope to measure intravascular Ca^{2+} concentrations by an IncyteIm2 instrument (Intracellular Imaging Inc, Cincinnati, OH, USA) by recording images (cutoff >510 nM) excited alternatively by 340 and 380 nm wavelengths. Images were recorded every 4 s and evaluated offline. Arterial Ca^{2+} concentrations were detected by calculating ratios (R) between averaged signal intensity at 340 and 380 nm excitation wavelengths in the whole arterial segment. Following the protocol of Nelson's group all the side-branches of the cerebral arteries were closed by pinching to prevent the Fura2-AM solution from diffusing into the vessel lumen where it could conceivably load the endothelium [185].

II.3.7. Statistical analysis

Experimental results are presented as mean ± S.E.M. Data are expressed as either micrometer or percentage of basal [BD%] and passive diameter [PD%]. The changes in ratiometric intracellular calcium measurements are indicated as a delta ratio (ΔR). Statistical analysis was performed after normality-test by one-way ANOVA (Holm-Sidak method) or Student's t-test as appropriate by SPSS 11.0 for Windows software. P-values <0.05 were considered to be statistically significant. Figures were made by SigmaPlot 11.0 for Windows software. Half-maximal concentrations (EC_{50}) were calculated from nonlinear regressions of the dose-response curves of nebivolol using SigmaPlot for Windows 11.0 software.

II.4. Results

II.4.1. Functional assessment of the endothelium removal and the vasomotor function of endothelium and smooth muscle of isolated basilar artery

In intact endothelium (E+) both the ACh and SNP elicited significant vasodilation. In endothelium-denuded (E-) arteries SNP caused dilation, while ACh did not affect diameters of BA. ATP caused acute biphasic vasomotor response of BA: first caused constriction, then dilation.

II.4.2. Effect of nebivolol on the diameter of isolated basilar artery

Increasing concentrations ($10^{-7} – 10^{-4}$ M) of nebivolol elicited significant dilations of BA. This finding and the EC_{50} range corresponds to those found by others [167, 182, 183], namely, that the EC_{50} of nebivolol is $7.8 \pm 0.2 \times 10^{-6}$ M. Thus we performed the experiments with specific inhibitors challenging the vasomotor effect of 10^{-5} M nebivolol.

II.4.3. Effect of inhibitors with known mechanisms of action on the nebivolol-induced dilation of isolated basilar artery

We found that L-NAME significantly reduced the basal diameter of BA. Neither ODQ, nor specific β_1-R antagonist atenolol, nor butoxamine, nor TEA, nor IBTX elicited significant changes in basal diameter of BA. SQ22536 induced significant increase in basal diameter of BA.

Nebivolol (10^{-5}M) elicited significant dilations of BA. Nebivolol-induced dilations of BA was not affected by ODQ, while the reduction of nebivolol-induced dilation increased with the following order: butoxamine, iberiotoxin, TEA, endothelium-denudation, L-NAME and SQ22536. Furthermore, atenolol completely eliminated the dilation to nebivolol.

II.4.4. Changes in $[Ca^{2+}]_i$ of isolated basilar artery in response to nebivolol

Nebivolol decreased the ratiometric Ca^{2+} signal (ΔR) in a concentration-dependent manner on BA. Nebivolol elicited dilations of basilar arteries with the consequent decrease in intracellular Ca^{2+} concentration.

II.4.5. Effect of nebivolol on the diameter of isolated basilar artery in the presence of hemolyzed blood

Perivascular hemolyzed blood elicits substantial constrictions of basilar arteries. Increasing concentrations of nebivolol in the presence of HB elicited dilation in a concentration-dependent manner, and in essence, completely reversed the constrictor effect of HB thus reached the basal diameter at a concentration of 10^{-5} M.

II.5. Discussion of findings

As far as we know, this is the first study to demonstrate that nebivolol elicits dilation of isolated cerebral arteries. Nebivolol seems to have specific regional effect, because the cerebrovascular dilation is mediated by several, parallel acting vasomotor mechanisms including $\beta_{1/2}$ adrenoceptors, endothelium-derived NO- and cAMP-linked mechanisms, hyperpolarizing factor(s)/ BK_{Ca} channels, finally, converging on the reduction of smooth muscle Ca^{2+} levels. In addition, nebivolol reversed the hemolyzed blood-induced constriction. Thereby nebivolol may be effective in the improvement of cerebral circulation in diseased conditions particularly in case of important need of reducing blood pressure with parallel vasodilation, thus providing adequate CBF and perfusion (**Fig 2.**).

II.5.1. Vasomotor effects of Nebivolol

It seems that the effects of nebivolol are organ/tissue specific, because in rat aortic rings Ignarro [167] found both endothelium-dependent and -independent mediation of relaxations, but several other mechanisms have been described underlying vasodilator effect of nebivolol. For example Evangelista et al. reported that antioxidant properties of nebivolol can increase the "surviving" level of NO by reducing its oxidative inactivation in human umbilical vein endothelial cells, and that $\beta_{1/2/3}$ adrenoceptors may play role in the development of nebivolol-induced dilation [186]. Moreover, Georgescu et al. showed nebivolol induces β_2 adrenoceptor-mediated and Ca^{2+}-activated potassium channel-induced hyperpolarization with the consequent relaxation in mice renal arteries [183], whereas, Tran-Quang et al. has demonstrated nebivolol-induced specific, either β_2 and β_3 agonist or α_1 and β_1 antagonist adrenoceptor-mediated relaxations in rat aortic rings [187]. It was also observed that nebivolol elicits the release of hyperpolarizing factor via activation of calcium-activated potassium channels [182] that - in part - maintains vessel relaxation when eNOS (endothelial NO synthase) is inhibited [167]. Such parallel and backup mechanisms would be particularly important, when NOS (NO synthase) activity, NO bioavailability, and/or other signaling mechanisms are impaired, such as increased oxidative stress and ischemic heart diseases [172-174].

II.5.2. Nebivolol induces dilation of cerebral arteries

Nebivolol is a 3rd generation widely used β-blocker [142-145] drug with antiarrhythmic and antihypertensive effect [143, 168] (Evidence I/A). In addition, it has been discovered that nebivolol has vasomotor effects, which seems to unrelated to its direct β_1 receptor mediated action. Namely in peripheral arteries nebivolol induces dilation [143, 148] in part, via increasing the activity of eNOS (endothelial nitric oxide synthase) thereby upregulating NO-cGMP (cyclic-guanylate monophosphate) pathway [167] resulting in vasodilation [170, 171].

Interestingly, as mentioned above, there are no data available regarding the vasomotor effects of nebivolol in cerebral vessels. Thus we aimed to characterize the dilator properties of nebivolol in isolated basilar arteries, in such conditions, in which the intraluminal pressure and extravascular environment were controlled. Based on previous studies [167, 182, 183, 187] we have used nebivolol in a range of 10^{-7} to 10^{-4} M which is in accordance with a range of concentrations used by others. Our data show significant dilations of BA in response to concentration-dependent administration of nebivolol. Since the EC_{50} is 7.8 ± 0.19 x 10^{-6} M, we performed measurements with specific inhibitors near this EC_{50} range in the presence of nebivolol arbitrarily at 10^{-5} M. Despite the calculated pharmacologically relevant plasma concentrations in humans after taking 5 mg nebivolol orally, it is in the nM range, but it still elicits a significant decrease in systemic vascular resistance [187], and it may result in dilation in human cerebral arteries. It is also possible that smaller cerebral vessels are even more sensitivity to nebivolol, as it is a general characteristics of microvessels that their sensitivity to various drugs and stimuli increases as the size (diameter) of vessels decreases [188].

II.5.3. Role of endothelium in nebivolol-induced dilation of basilar artery

It is well known endothelium is an important active mechanical and biological interface between the circulating blood and surrounding tissues. It has many special function from gas exchange to vasomotor [189] and barrier function. Vasomotor function of endothelium includes sensing of wall shear stress associated with blood flow velocity changes and other autocrine and paracrine signal transductions mechanism and substances [190] [191]. Thus in many instances, removal or impairment of endothelium has a significant influence on vasomotor tone and function. In the present study we have confirmed previous findings that absence of endothelium significantly decreased the basal diameter of cerebral arteries, supporting a putative role for maintaining basal tone [2, 122, 123]. Nebivolol-induced cerebral vasodilation significantly decreased in absence of endothelium, supporting the role of endothelium in the development of nebivolol-induced dilation. It corresponds to those found by others [165, 167-171, 183].

II.5.4. Role of NO in maintaining basal tone of BA

Results coming from aforementioned investigations demonstrated a special role of NO in maintaining basal tone. As previously described [130], we have also confirmed that in basilar arteries endogenous NO (produced by endothelium) contributes to the development of basal vascular tone as administration of L-NAME significantly decreased the basal diameter, supporting previous findings [1, 178], and underlying the physiological importance of NO in the regulation of vasomotor tone of cerebral arteries [2, 122, 123].

II.5.5. Role of eNOS-NO and cGMP/cAMP pathways in the development of nebivolol-induced dilation

Previous studies showed that the basal tone of ***peripheral arteries*** is modulated by NO [129, 192, 193] and that nebivolol induces an eNOS/NO-mediated dilations in peripheral arteries [167-171]. In the recent study we have found that presence of eNOS blocker L-NAME significantly decreased the basal diameter of ***basilar artery*** in accordance with previous studies [130-133]. More importantly, we found that the dilations of isolated rat basilar arteries to nebivolol was also reduced in the presence of L-NAME, suggesting that NO is involved in the mediation of the response.

Most previous studies suggest that NO increases the level of the smooth muscle soluble guanylate cyclase (sGC) enzyme producing cyclic-guanylate monophosphate (cGMP). Then, cGMP activates protein kinase-G (PKG) [194], which is responsible for inactivating the myosin light chain kinase (MLCK). MLCK would be the essential enzyme in the development of vasoconstriction, which is inhibited by elevated level of PKG thus resulting in dilation [195].

In addition, previous studies assigned an important role for the cyclic-adenosine monophosphate (cAMP) produced by adenylyl cyclase (AC) mechanism in mediation of various dilator responses of vessels [196]. cAMP can 1) activate protein kinase-A (PKA) thereby inactivating MLCK resulting in dilation, 2) activate calcium ATPase thus reducing $[Ca^{2+}]_i$ leading to vasodilation, 3) inhibit calcium-calmodulin complexes thereby inducing vasodilation. Therefore we performed experiments to block synthesis of both cAMP [180] (with SQ22536) and cGMP (with ODQ).

In contrast to previous studies (canine coronary and pulmonary arterial rings, human forearm) [167, 169-171], but similarly to Ogawa et al. [197], we have found that the sGC-inhibitor ODQ did not decrease the basal diameter, and did not reduce the nebivolol-induced dilations suggesting that intracellular sGC/cGMP pathway does not contribute significantly to the development of nebivolol-induced dilations of cerebral arteries. We explain these findings by the presence of sGC/cGMP independent NO pathway(s) [197-204]. Indeed, there is evidence that in certain vessels the vasodilator effect of NO are mediated via COX-dependent, cAMP mediated pathway [197, 202-204], for example in rat retinal blood vessels [197, 198] that are ontogenetically are closely related to cerebral vessels. However, it has also been shown that NO can act directly to Ca^{2+}-dependent K^+ channels in vascular smooth muscle cells, which cause a dilator response [199, 201] or by decreasing Ca^{2+}-sensitivity of arteriolar smooth muscle [184].

Our data shows that AC inhibitor SQ22536 exhibited significant increase in basal diameter suggesting the presence of a tonic release of a constrictor factor and/or SQ22536 may elicit nonspecific enzyme inhibition [205]. Yarova et al. showed that β_1-agonist in presence of endogenous/exogenous inductor (acetylcholine) suppresses vasodilation via increase in endothelial cAMP level [206]. If endothelial AC is blocked it can mimic the β_1-

antagonist-induced vasodilation, supporting the findings that dilation was observed in the presence of SQ22536. In the presence of SQ22536 nebivolol-induced dilation was significantly reduced, suggesting the involvement of an AC/cAMP, rather than a sGC/cGMP mechanism in the development of nebivolol-induced dilation of basilar arteries, which seems to be activated by NO. These results are in agreement with findings of others [197], which showed that in certain vessels NO acts via the cAMP pathway, including COX1-PGI_2/PGE_2-Gs pathways [197, 198, 202-204]. Thus we propose that cerebrovascular dilator effects of nebivolol depend - in part - on endothelial mechanisms and the eNOS/NO-AC/cAMP pathway.

II.5.6. Involvement of β-adrenoceptor and BK_{Ca} channels in the development of nebivolol-induced dilation of BA

Cekic et al. showed the specific β_1 adrenerg antagonist atenolol did not elicit relaxation of rat cerebral arteries, whereas the non-selective propranolol induced relaxation [175]. Tran-Quang et al. demonstrated β_1 receptor antagonist did not affect significantly the nebivolol-induced relaxation in rat aortic rings, suggesting β_1 receptors do not contribute to the development of nebivolol-induced dilation [187]. Interestingly, Yarova et al. showed on rat mesenteric arteries that endothelial β-adrenoceptor agonists decreased ACh-induced dilation, whereas in the presence of β_1-antagonist atenolol, ACh-induced dilation remained intact [206]. These findings raise the possibility that specific β_1 adrenoceptor antagonist - in certain circumstances - may have the characteristics of functional agonist, via blocking endothelial Gs-AC-cAMP-PKA pathway, thereby decreasing the inactivation of Ca^{2+}-dependent potassium channels, resulting in endothelial and smooth muscle hyperpolarization (through myoepithelial gap junction), leading to vasodilation [206].

In the present study we show that β_1 selective antagonist atenolol did not significantly affect basal diameter of BA, which may be due to either absence of an endothelial inductor factor [175], or it may have parallel β_2 receptor antagonist properties, as Nuttall reported [207]. Furthermore we found that atenolol almost completely eliminated the dilations to nebivolol, which can be explained by either the presence of a β_2-antagonist effect of atenolol (resulting in inhibition of dilation) [207] or by occupying β_1 adrenoceptors (competitive antagonism), when nebivolol could act in presence of NO. Accordingly, one can suggest that nebivolol-induced dilation is attributed – in part – via β_1 adrenoceptors.

Studies of Georgescu et al. [183], suggest that β_2 adrenoceptors may play important role in the development of nebivolol-induced dilation in mice renal artery. This prompted us to investigate the potential mediating role of β_2 adrenoceptors in the vasomotor action of nebivolol in basilar artery. β_2 adrenoceptor antagonist butoxamine (BTXN) significantly decreased the nebivolol-induced dilations of BA. β_2 receptors may be expressed both on endothelial cell and on vascular smooth muscle cell. The endothelium-dependent, NO mediated pathway may be one of the major functions of β_2 receptors. Stimulation of β_2 receptors (expressed on vascular smooth muscle cells) leads to the activation of AC-cAMP-PKA pathway, which induces dilation - in part - by inactivating MLCK and partly by activating BK_{Ca} channels [208] and hyperpolarization.

Bolotina et al. demonstrated the involvement of BK_{Ca} channels in NO-mediated vasodilation [199] and Georgescu et al. showed the role of BK_{Ca} channels in the development of nebivolol-induced dilation [182]. In line with previous findings, our results showed that the BK_{Ca} channel antagonist iberiotoxin [IBTX] and TEA significantly reduced nebivolol-induced dilation, suggesting an important role of BK_{Ca} and hyperpolarization, mediated by endothelial NO, and cAMP-PKA, and via β_1 and β_2 receptor mediated pathways, which seem to be specific for cerebral arteries.

II.5.7. Nebivolol decreases $[Ca^{2+}]_i$ in basilar arteries

Previous studies also suggested that therapeutic effects of β-blockers could be attributed to endothelium-independent mechanisms [175-177]. Sakanashi et al. found propranolol-induced relaxation in canine coronary arteries and raised the possibility that propranolol reduces the calcium-influx [177]. Priviero et al. showed that propranolol-induced relaxation in rat aorta and mesenteric artery may occur, independent of β-adrenoceptor blockade, via inhibition of calcium influx [176]. Similarly, Cekic et al. suggested, that nonspecific β-blocker propranolol exhibited calcium antagonist activity in rat basilar arteries [175]. Since we have found that nebivolol elicits dilation of basilar arteries, we hypothesized that regardless of proximal pathways, nebivolol reduces the Ca^{2+} level in smooth muscle, which then results in dilation. Thus we investigated parallel changes in the vascular Ca^{2+}-signal (R) and the diameter in isolated basilar arteries utilizing the ratiometric method used in our previous studies and others [38, 82-84]. The data of present study show that increasing concentrations of nebivolol caused significant decrease in vascular Ca^{2+}-signal (R), indicating decrease in vascular $[Ca^{2+}]_i$ concentration. The decrease in ratiometric Ca^{2+}-signal and the consequent dilation suggest that the signal is coming primarily from the vascular smooth muscle layer. This is congruent with our functional measurements of diameter changes and suggests that the final signaling mechanism by which nebivolol elicits dilation of cerebral arteries is the reduction of smooth muscle intracellular Ca^{2+} concentration.

II. 5.8. Reversal of hemolyzed blood-induced constriction of isolated BA

In recent study we have found that perivascular hemolyzed blood induces substantial constriction of isolated basilar arteries by increasing smooth muscle $[Ca^{2+}]_i$ [38]. Regarding the complex mechanisms of action, impairment of NO-mediated endothel- and smooth muscle-dependent mechanisms and multifactorial origin of HB-induced vasoconstriction, we have investigated the possible mechanisms of recovery of basal diameter of cerebral arteries, including CO_2, Ca^{2+}-channel blockers and wash-out methods. Furthermore, nebivolol elicits significant and

functional considerable vasodilation via complex mechanism of action, thus we proposed that nebivolol may have Ca^{2+}-antagonist properties. Thereby we have tested the dilator effect of nebivolol in the presence of perivascular hemolyzed blood. Interestingly, we have found that hemolyzed blood (HB)-induced constriction of cerebral arteries could be reversed by increasing concentrations of nebivolol. It has to be noted that nebivolol restored the HB-induced vasoconstriction at a concentration of 10^{-5} M, referring to significant vasomotor effect at relevant EC_{50} value, and Ca^{2+}-antagonist properties of nebivolol. This finding strongly suggests that nebivolol have potential therapeutic value, for example, in patients with subarachnoid hemorrhage-induced cerebrovascular spasm.

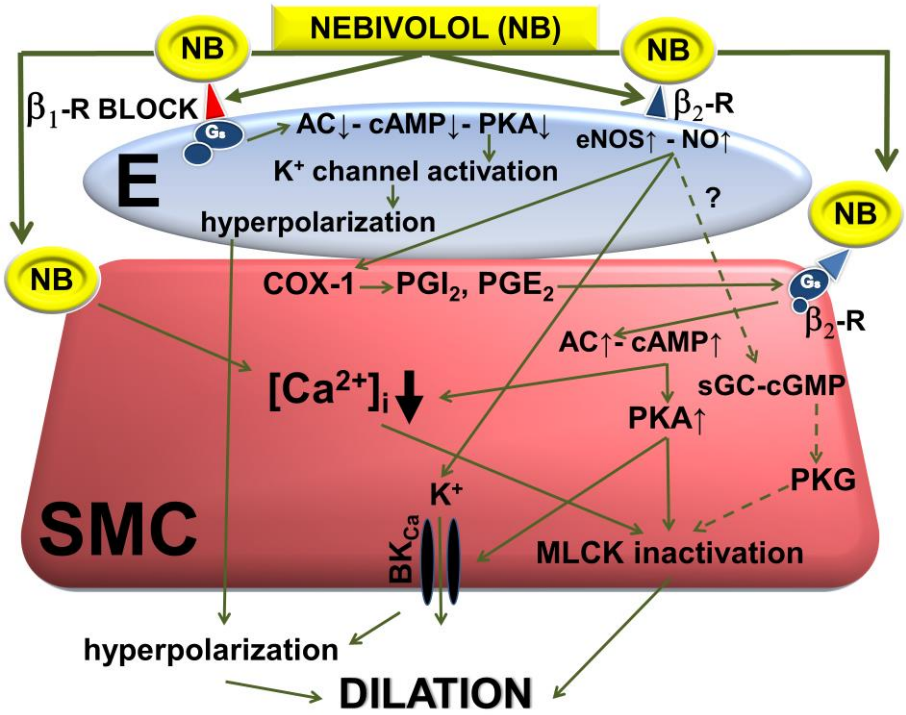

Fig 2. Proposed mechanisms of action of nebivolol (NB)-induced dilation of cerebral arteries

(E, endothelium; SMC, vascular smooth muscle cell). These findings demonstrate that: 1) in isolated cerebral arteries nebivolol elicits significant dilations, 2) which may be - in part - due to β_2 adrenoceptor (β_2-R) mediated, endothelium-dependent NO and cAMP mechanisms resulting in either reduced $[Ca^{2+}]_i$, and smooth muscle hyperpolarization. 3) On the other hand, its action seems to be mediated - in part - by β_1 (β_1-R) specific blocking ability connected with parallel induced vasodilation with endothelium derived hyperpolarization. 4) Contribution of cGMP and other ion channels seem to be less important. These findings can contribute to a better understanding of the complex effects of this β_1-receptor blocker on cerebral circulation and implicate important novel therapeutic potentials to improve cerebral blood flow in diseased conditions.

II.5.9. Clinical implications

Searching for effective pharmaceutical treatments to improve cerebral blood flow in diseased conditions or during aging is an ongoing effort in clinical practice. In ischemic condition, such as transient ischemic effect [209] or stroke (ischemic [210], hemorrhagic [127]) the resistance of cerebral vessels greatly increases thus reducing the adequate cerebral blood flow. Our findings show sizeable dilations of basilar cerebral arteries to nebivolol in the absence of neural or other tissue factors.

The similarity in vascular responses indicates that the rat model is a good surrogate for the human model when conducting vasodilator experiments [211]. Extrapolating these experimental findings to clinical area, may open up novel therapeutic possibilities for this novel 3rd generation β_1-blocker. It has to be noted that based on previous studies, malignant arrhythmias may occur in acute phase of SAH, which deteriorate the prognosis and indicates monitoring [23].

A previous trial (BEST) using propranolol to assess its effects on cerebral function in patients with subarachnoid hemorrhage and those suffering from acute stroke showed promising improvement in the long range, but more early death [212]. Nebivolol has been shown to be very safe and effective β_1-blocker [213] and is used in much lower concentration than propranolol [205], thus one can assume that it may have less side effects in transient ischemic attack (TIA) or in various stroke conditions. Our data show that nebivolol significantly and functional considerably increased diameters of cerebral arteries even in the presence of perivascular blood.

Nebivolol seems to be an appropriate antihypertensive medication in hemorrhagic stroke or in patients with SAH-induced vasospasm following endovascular treatment of bleeding cerebral aneurysms [214]. Thus by dilating cerebral arteries, nebivolol may be useful in stroke patients providing adequate CBF and restoring cerebral perfusion, particularly in case of important need of reducing blood pressure with parallel vasodilation with antiarrhythmic properties. Future clinical studies are needed to elucidate this possibility and document the beneficial effects of nebivolol on cerebral circulation in various diseased conditions.

II.6. Summary of novel findings of Part II

1. This is the first study showing that nebivolol induces significant and substantial dilation of cerebral arteries in a concentration-dependent manner.
2. Nebivolol-induced vasodilation is mediated by several parallel intracellular pathways,
3. including β_2 adrenerg receptors, endothelium-derived NO and cAMP linked mechanisms,
4. that are all seem to converge on the reduction of $[Ca^{2+}]_i$, level and/or hyperpolarization of smooth muscle cell via BK_{Ca} channels.
5. β_1 specific binding site seems to be important in nebivolol-induced vasodilation.
6. These functional vasomotor responses correlates with changes in vascular Ca^{2+}-signal.
7. Nitric oxide plays an important role in the regulation of vasomotor tone of cerebral arteries.
8. Nebivolol elicited significant and substantial vasodilation even in the presence of perivascular hemolyzed blood, furthermore reversed the constrictor effect of HB, which was shown earlier to increase smooth muscle Ca^{2+}, implicating important novel therapeutic potentials.

II.7. Connections in the content of the Thesis

In the beginning our experiments have been divided, but the presence of interdependent network and junctions of heterogeneous pathophysiological conditions it has developed a joint important relationship.

Searching for effective pharmaceutical treatments to improve cerebral blood flow in diseased conditions is an ongoing effort in clinical practice, particularly in ischemic conditions or in case of SAH-induced vasospasm. During these conditions the cerebrovascular resistance greatly increases thus reducing regional CBF and impair parenchymal arterial functions. Our results show that direct perivascular hemolyzed blood (in the absence of neural or other tissue factors) elicited vasoconstriction that could be prevented by Ca^{2+}-channel blocker and elevated CO_2 level or by wash-out of blood or by using nebivolol. We propose that our results may contribute to a better understanding of complex mechanism of action of the β_1-receptor blocker nebivolol. Extrapolating these experimental findings to clinical area, may open up novel important therapeutic possibilities in the improvement of cerebral blood flow in pathological conditions, such as in case of subarachnoid hemorrhage. In addition raise the possibility of optimization of impaired cerebrovascular blood flow, particularly in case of important need of reducing blood pressure with parallel vasodilation with antiarrhythmic properties, thereby providing adequate CBF and restoring cerebral perfusion.

It has to be noted as a conclusion that as far as we know, this is the first study that reveal the -previously unknown- cerebrovascular effects of hemolyzed blood and a β_1-receptor blocker. Our data may serve by itself or together as a basis for further research that may be important in everyday practice for healing.

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IV. List of publications

IV.1. Publications in peer-reviewed journals (in English)

The thesis is based on the following publications:

1. **Cseplo P**, Vámos Z, Torok O, Ivic I, Toth A, Buki A, Koller A: Hemolyzed blood elicits - calcium antagonist and high CO2 reversible - constrictions via elevation of Ca^{2+} in isolated cerebral arteries; J Neurotrauma. 2016 May 26. [Epub ahead of print] PMID: 27018759; doi: 10.1089/neu.2015.4365 ***(IF: 4,377)***
2. **Cseplo P,** Vamos Z, Ivic I, Torok O, Toth A, Koller A: The beta-1-receptor blocker nebivolol elicits dilation of cerebral arteries by reducing smooth muscle $[Ca^{2+}]_i$; PLoS One. 2016 Oct 7;11(10):e0164010. doi: 10.1371/journal.pone.0164010. PMID: 27716772 ***(IF: 3,234)***

Other publications:

3. Ivic I, Vamos Z, **Cseplo P**, Koller A: Morphological and functional remodeling of arteries from newborn to senescence leads to increased contractile capacity; J Gerontol A Biol Sci Med Sci.; J Gerontol A Biol Sci Med Sci. 2016 May 17. pii: glw085. doi: 10.1093/gerona/glw085 [Epub ahead of print] ***(IF: 5,416)***
4. Vamos Z, Ivic I, **Cseplo P**, Toth G, Tamas A, Reglodi D, Koller A: Pituitary adenylate cyclase-activating polypeptide (PACAP) induces relaxations of peripheral and cerebral arteries, which are differentially impaired by aging; J Mol Neurosci. 2014 Nov;54(3):535-42. doi: 10.1007/s12031-014-0349-9. Epub 2014 Jun 19.PMID: 24939249 ***(IF: 2,343)***
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8. Toth P, Csiszar A, Sosnowska D, Tucsek Z, **Cseplo P**, Springo Z, Tarantini S, Sonntag WE, Ungvari Z, Koller A: Treatment with the cytochrome P450 ω-hydroxylase inhibitor HET0016 attenuates cerebrovascular inflammation, oxidative stress and improves vasomotor function in spontaneously hypertensive rats; Br J Pharmacol. 2013 Apr;168(8):1878-88. doi: 10.1111/bph.12079. PMID: 23194285 ***(IF: 4,990)***
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Cumulative impact factor of original publications in peer-reviewed journals: **32,429**
Independent citations: **41**
Cumulative impact factor of citable publications: **149,077**
Number of citable abstarcts: **64**

IV.2. Citable publications (in Hungarian)

1. Vámos Z, **Cséplő P**, Koller Á: Az életkor hatása a vaszkuláris renin–angiotenzin rendszer működésére. Hypertonia és Nephrologia 16(5):187-200 (2014).
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IV.3. Chapter publications

1. Ezer Erzsébet, **Cséplő Péter**, Vámos Zoltán: Súlyos koponyasérültek primer ellátása; In: Komoly Sámuel (szerk.) Emberi életfolyamatok idegi szabályozása – a neurontól a viselkedésig. Interdiszciplináris tananyag az idegrendszer felépítése, működése és klinikuma témáiban orvostanhallgatók, egészség- és élettudományi képzésben résztvevők számára Magyarországon. 2299 p. ; Pécs: Dialóg Campus Kiadó, 2014. pp. 1900-1919.; (ISBN:978-963-642-631-6)
2. Ezer Erzsébet, **Cséplő Péter**, Vámos Zoltán: Primary treatment of severe neurotrauma. Neural regulation of human life processes – from the neuron to the behaviour. Interdisciplinary teaching material concerning the structure, function and clinical aspects of the nervous system for students of medicine, health and life sciences in Hungary, 2014: p. 1876-1895.
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IV.4. Citable abstracts (in English)

1. Akos Koller, Orsolya Torok, Zoltan Vamos, **Peter Cseplo:** In Vitro Model of Brain Trauma: in Isolated Basilar Artery Hemolysed Bloodinduced Constriction is Inhibited by Calcium Channel Blocker and Increased CO2; FASEB JOURNAL 29**:**(1) Paper 832.8. (2015) ***(IF:5,043)***
2. **P Cseplo**, Z Vamos, I Ivic, G Toth, A Tamas, D Reglodi, A Koller: Pituitary adenylate cyclase-activating polypeptide (PACAP) induces location- and age-related relaxations of isolated arteries; ACTA PHYSIOLOGICA 211: p. 97. (2014) ***(IF: 4,382)***
3. **Peter Cseplo**, Zoltan Vamos, Istvan Batai, Orsolya Torok, Zsolt Springo, Attila Toth, Akos Koller: Nebivolol reduces intracellular Ca2+ and elicits dilations in isolated rat basilar arteries; FASEB JOURNAL 28:(1) Paper 1070.7. (2014) ***(IF:5,043)***
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