SARS-CoV-2 Infection and Valproic Acid

Subjects: Infectious Diseases

Contributor: Donatas Stakišaitis , , Angelija Valančiūtė , Ingrida Balnyte , and Vacis Tatarunas , Dovydas Gecys , Vaiva Lesauskaite

The histone deacetylase inhibitor valproic acid (VPA) is a potential drug that could be adapted to prevent the progression and complications of SARS-CoV-2 infection. VPA has a history of research in the treatment of various viral infections. VPA inhibits SARS-CoV-2 virus entry, suppresses the pro-inflammatory immune cell and cytokine response to infection, and reduces inflammatory tissue and organ damage by mechanisms that may appear to be sex-related. The antithrombotic, antiplatelet, anti-inflammatory, immunomodulatory, glucose- and testosterone-lowering in blood serum effects of VPA suggest that the drug could be promising for therapy of COVID-19. Sex-related differences in the efficacy of VPA treatment may be significant in developing a personalised treatment strategy for COVID-19.

valproic acid COVID-19

1. SARS-CoV-2 Virus and VPA

The docking, binding energy calculation determines that VPA metabolite 4-ene-VPA-CoA creates a stable interaction with nsP12 of SARS-CoV2 RNA polymerase and VPA-CoA could specifically inhibit the target. SARS-CoV-2 RNA polymerase is an enzyme playing in viral RNA replication and the virus's survival in a host [1][2]. The SARS-CoV-2 virus x-ray crystal structure of a critical protein in the virus's life cycle is the central protease (M^{pro}, $3CL^{pro}$) [3][4][5]. The M^{pro} importance recognises M^{pro} as a target for antiviral drugs, designed as a virus $3CL^{pro}$ inhibitor, for COVID-19 therapy [6][7]. HDACs' inhibitors are tightly bound into the active site of the crystallographic virus M^{pro} structure [8]. The SARS-CoV-2 protease NSP5 interacts with the HDAC2. Researchers predict that NSP5 may inhibit the transportation of HDAC2 into a nucleus, and could affect the HDAC2 strength to interfere with the interferon response and inflammation [9][10]. Experimental studies show that the binding of HDAC2 to the promoters was lower in females than in males [11]. The HDAC2 activity can not only be modulated by VPA binding to the catalytic center, but the HDAC2 protein level is susceptible to selective regulation by VPA [12]. VPA blocks the zinc-containing catalytic domain of HDACs [13]. VPA treatment reduced HDAC2 level in male rats' brain frontal cortex tissue, but no VPA effect was for HDAC2 protein in females [14].

2. Sex-Related COVID-19 Infection Progression Mechanisms and VPA

Due to the high viral infection load, membrane ACE2 and its mRNA expression are significantly diminished in COVID-19 patients [15][16][17][18]. At a later COVID-19 infection stage, down-regulated ACE2 in tissues may worsen

the imbalance in the renin-angiotensin system (RAS). ACE2 has a protective effect through RAS regulation [19], and protects against RAS-mediated activations of harmful effects [15][20]. Depleting ACE2 in tissue cells leads to an increase in angiotensin II (Ang II) blood serum level and the activation of the AT_1 receptors, which would activate ADAM17 more. The ACE2 expression is transcriptionally suppressed due to AT_1 activation [21]. Increased Ang II levels act as a vasoconstrictor and a pro-inflammatory molecule through AT_1 [22]. ACE2 knockout results in pathology similar to the acute respiratory distress syndrome in mice [23]. The ACE2 molecule reduces RAS activity by converting Ang II into Ang 1–7 [24][25][26], decreasing Ang II level and the AT1 activation, which manages reduced pathological inflammation effects in tissues [15][27][28]. Sex distinctions of the RAS in response to stimulation and inhibition of the system have been reviewed [29][30][31]. Higher levels of ANG (1–7) in women may inhibit the harmful effects of ANG II and its activation [32]. Compared with female rats, males have higher AT1 receptor RNA, higher AT1 protein levels, higher receptor density in kidneys and ~40% higher specific AT1 binding in the glomeruli than females. These differences are 17β-estradiol (E2) dependent [29][31][33]. Activation of AT1 mediates ANG II's biological functions, such as sodium reabsorption, vasoconstriction, increased oxidative stress and inflammation [34][35]. VPA, inhibiting HDAC1 and HDAC2, down-regulates Ang II and AT1 activity [36][37]. VPA reverses the ANG II-induced increment of HDAC2 RNA and protein levels in cardiomyocytes [38]. Anti-hypertensive action of VPA is mediated by the inhibition of HDAC1 via acetylation processes [36][39].

3. COVID-19 Thrombotic Complications and VPA

3.1. SARS-CoV-2 and Sex-Related Thrombotic Complications

The pathophysiology of COVID-19 complications is characterised by clinical features of thrombosis and disseminated intravascular coagulopathy in the airways, myocardium, kidneys, brain and other organs [40]. Thrombosis is found in approximately 30% of COVID-19 hospitalised patients [41]. The incidence of thrombosis in COVID-19 is higher in men than in women and explains the higher mortality in men [42]. In an analysis of 29 studies, 70% of all thromboembolic events occurred in men and 30% in women [43]. Viral invasion due to severe vascular endothelial damage triggers the coagulation cascade, impairs fibrinolytic activity, releases von-Willebrand factor [44], increases total cytokine release, activates platelets and the complement system and generates thromboxane [45][46]. SARS-CoV-2 can directly activate coagulation via the viral M^{pro}; the active site of M^{pro} is structurally similar to the active site of FXa and thrombin and can therefore activate coagulation [47]. The development of thrombosis has been attributed to the direct effects of the virus by increasing the levels of pro-inflammatory cytokines and pro-inflammatory M1 macrophages, by activation of the complement system and by endothelial dysfunction, leading to disseminated intravascular coagulopathy [48][49][50][51]. Endothelial dysfunction and its association with thrombosis have been implicated in SARS-CoV-2-induced target organ damage [52]. VPA binding to SARS-CoV-2 M^{pro} is expected to inhibit M^{pro} pathways [53]. Older men with hypertension, chronic kidney disease, coronary disease, diabetes mellitus and obesity are at increased risk of thrombotic complications [54][55][56]. Changes in plasma levels of D-dimer, von Willibrand factor (vWF), fibrinogen, tissue-type plasminogen activator (t-PA), plasminogen activator inhibitor-1 antigen (PAI-1) antigen are associated with poorer outcomes in COVID-19 patients [57][58][59][60].

3.2. VPA Effect on Thrombosis Mechanisms, COVID-19

The VPA effects on thrombogenesis have been explored in pre-clinical studies and during the treatment of patients with VPA (**Table 1**). HDAC inhibitors have reduced platelet counts and inhibit platelet function [61][62], while other VPA experimental and clinical trials did not find such effects [63][64]. The baseline platelet count was similar in women and men. A causal relationship between prolonged use and rising plasma VPA levels and reduced platelet counts, with reversal of thrombocytopenia after reduction of VPA dosage, was reported: that of thrombocytopenia substantially increased at VPA levels above 100 ug/mL in women and above 130 ug/mL in men; women were significantly more likely to develop thrombocytopenia [65]. There is a significantly higher female overrepresentation in heparin-induced thrombocytopenia, with females at approximately twice the risk of thrombocytopenia than males. However, the underlying mechanism for this sex difference is unclear [66]. VPA may affect several different coagulation factors: decrease in von Willebrand factor:antigen (vWF:Ag) concentration [67][68]; protein C level [67][69], protein S level [69][70], antithrombin III level, decrease prothrombin time [67][68] and increase activated partial thromboplastin time [67][68][69].

Table 1. VPA treatment effect on thrombogenesis.

#	Thrombogenesis Related Factor	Cells/Animals/Human	Sex	VPA Treatment Effect	Ref.
1.	Complement C3	HepG2 cells	unknown	↓ *C3* gene expression	[71]
2.	t-PA	Human umbilical vein endothelial cells	unknown	↑ t-PA production	[72]
3.	ICAM-1 expression	Human umbilical vein ECs and human coronary artery EC	unknown	↓ ICAM-1 expression	[73]
4.	Platelets number	C57BL/6 mice	unknown	↓ platelets count	[62]
5.	Vascular t-PA	C57BL/6 mice	males	↑ endothelial vascular t-PA production; ↓ fibrin accumulation in response to vascular injury	[63]
6.	E-selectin and ICAM-1	Sprague–Dawley rats with subarachnoid hemorrhage induced vasospasm	males	↓ the E-selectin and ICAM-1 level	[74]
7.	Platelets number	Epileptic adult patients and healthy control	men and women	relationship between rising plasma VPA level and reduced platelet counts, with female sex additional risk factor	[65]

#	Thrombogenesis Related Factor	Cells/Animals/Human	Sex	VPA Treatment Effect	Ref.
8.	Arachidonate cascade thromboxane A2 in platelets	Epileptic adult patients and healthy control	men	↓ activity of the arachidonate cascade in platelets; ↓ the cyclooxygenase pathway; ↓ synthesis thromboxane A2	[61]
9.	Von Willebrand factor:antigen	Epileptic children patients and healthy control	male + female (combined)	↓ concentration in blood serum	[67] [68]
10.	Protein C	Epileptic children patients and healthy control	male + female (combined)	↓ concentration in blood serum	[67] [69]
11.	Protein S	Epileptic children patients and healthy control	male + female (combined)	↓ concentration in blood serum	[69] [70]
12.	Antithrombin III	Epileptic children patients and healthy control	male + female (combined)	↓ concentration in blood serum	[67] [68]
13.	Prothrombin time	Epileptic children patients and healthy control	male + female (combined)	↓ concentration in blood serum	[67] [68]
14.	Activated partial thromboplastin time	Epileptic children patients and healthy control	male + female (combined)	↓ concentration in blood serum	[67] [68] [69]

Activated
COVID-19
d C5a are
significant contributors to the cytokine storm syndrome [77]. The healthy adult population is characterised by substantial sex-related differences in complement levels and function: significantly lower AP activity was in females than males. AP revealed lower C3 levels in women [78]. In experimental intestinal ischemia with an acute inflammatory response, complement activity was sex-dependent: female MBL-/- and P-/- mice had significantly less C5a in their serum than males [79]. Experimental results indicate that lysine acetylation by VPA is associated with attenuated C3 gene expression. VPA-associated reductions in circulating complement and clotting factors result from changes in liver-specific gene expression [71]. VPA inhibits intercellular adhesion molecule-1 (ICAM-1) and E-selectin [73][74]. Analysis from patients hospitalised with COVID-19 showed higher circulating VCAM-1 and E-selectin levels in men than women [80]. The endothelial cell adhesion molecules elevated levels promote tissue infiltration of circulating leukocytes and are associated with inflammation and thrombosis, which occur at a higher frequency in males [81]. VPA reduced endothelial cell dysfunction through the mechanisms of action of transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF) in a porcine model of ischemia-reperfusion of hemorrhagic shock [82]. Inhibiting TGF-β activity, VPA alleviates pulmonary fibrosis through epithelial-mesenchymal transition inhibition in vitro and in vivo [83]. Estradiol has been shown to decrease TGF-β1 synthesis [84]. VPA inhibiting IL-12 and TNF-α, reversing macrophage polarisation from pro-inflammatory to the anti-inflammatory type, and reducing macrophage infiltration reduces the risk of thrombosis [85][86].

3.3. VPA and Fibrinolysis

Treatment with VPA in a rat thrombosis model reduced thrombus formation and did not increase bleeding tendency [63]. VPA can selectively manipulate the fibrinolytic system to reduce thrombus formation in blood vessels in vivo. In a murine model of thrombosis induced by intravascular injury, VPA treatment increased t-PA production in blood vessels [63][72][87][88][89] was associated with less fibrin accumulation and fewer thrombi [63][90]. Impaired fibrinolysis, due to reduced t-PA production and depleted storage or increased expression of a significant inhibitor of fibrinolysis PAI-1 [91][92], has been reported in coronary heart disease patients with cardiovascular risk factors, such as hypertension and obesity [93][94][95][96][97]. A clinical trial of VPA treatment showed a significant reduction in PAI-1 and signs of improvement in fibrinolysis, favourably altered the balance between t-PA and PAI-1, and the dose of VPA treatment was significantly lower than the usual dose of VPA for epilepsy [64][89][90]. Thus, VPA could be a potential alternative for preventing thrombotic events based on improved endogenous fibrinolysis [64].

References

1. Zhou, P.; Yang, X.-L.; Wang, X.-G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.-R.; Zhu, Y.; Li, B.; Huang, C.-L.; et al. A Pneumonia Outbreak Associated with a New Coronavirus of Probable Bat Origin. Nature 2020, 579, 270–273.
2. Bhavesh, N.S.; Patra, A. Virtual Screening and Molecular Dynamics Simulation Suggest Valproic Acid Co-A could Bind to SARS-CoV2 RNA Depended RNA Polymerase. Preprints 2020, 2020030393.
3. Mengist, H.M.; Fan, X.; Jin, T. Designing of Improved Drugs for COVID-19: Crystal Structure of SARS-CoV-2 Main Protease Mpro. Signal Transduct. Target. 2020, 5, 67.
4. Elfiky, A.A. Anti-HCV, Nucleotide Inhibitors, Repurposing against COVID-19. Life Sci. 2020, 248, 117477.
5. Elfiky, A.A. Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA Dependent RNA Polymerase (RdRp): A Molecular Docking Study. Life Sci. 2020, 253, 117592.
6. Jin, Z.; Du, X.; Xu, Y.; Deng, Y.; Liu, M.; Zhao, Y.; Zhang, B.; Li, X.; Zhang, L.; Peng, C.; et al. Structure of Mpro from SARS-CoV-2 and Discovery of Its Inhibitors. Nature 2020, 582, 289–293.
7. Pillaiyar, T.; Manickam, M.; Namasivayam, V.; Hayashi, Y.; Jung, S.-H. An Overview of Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV) 3CL Protease Inhibitors: Peptidomimetics and Small Molecule Chemotherapy. J. Med. Chem. 2016, 59, 6595–6628.
8. Mohamed, M.F.A.; Abuo-Rahma, G.E.A.; Hayallah, A.M.; Aziz, A.M.; Nafady, A.; Samir, E. Molecular Docking Study Reveals The Potential Repurposing Of Histone Deacetylase Inhibitors Against COVID-19. Int. J. Pharm. Sci. Res. 2020, 18, 4261–4270.

9. Barnes, P.J. Role of HDAC2 in the Pathophysiology of COPD. Annu. Rev. Physiol. 2009, 71, 451–464.
10. Dewe, J.M.; Fuller, B.L.; Lentini, J.M.; Kellner, S.M.; Fu, D. TRMT1-Catalyzed tRNA Modifications Are Required for Redox Homeostasis To Ensure Proper Cellular Proliferation and Oxidative Stress Survival. Mol. Cell. Biol. 2017, 37, e00214-17.
11. Matsuda, K.I.; Mori, H.; Nugent, B.M.; Pfaff, D.W.; McCarthy, M.M.; Kawata, M. Histone Deacetylation during Brain Development Is Essential for Permanent Masculinization of Sexual Behavior. Endocrinology 2011, 152, 2760–2767.
12. Krämer, O.H.; Zhu, P.; Ostendorff, H.P.; Golebiewski, M.; Tiefenbach, J.; Paters, M.A.; Brill, B.; Groner, B.; Bach, I.; Heinzel, T.; et al. The Histone Deacetylase Inhibitor Valproic Acid Selectively Induces Proteasomal Degradation of HDAC2. EMBO J. 2003, 22, 3411–3420.
13. Dokmanovic, M.; Clarke, C.; Marks, P.A. Histone Deacetylase Inhibitors: Overview and Perspectives. Mol. Cancer Res. 2007, 5, 981–989.
14. Tyler, C.R.S.; Smoake, J.J.W.; Solomon, E.R.; Villicana, E.; Caldwell, K.K.; Allan, A.M. Sex-Dependent Effects of the Histone Deacetylase Inhibitor, Sodium Valproate, on Reversal Learning After Developmental Arsenic Exposure. Front. Genet. 2018, 9, 200.
15. Gheblawi, M.; Wang, K.; Viveiros, A.; Nguyen, Q.; Zhong, J.-C.; Turner, A.J.; Raizada, M.K.; Grant, M.B.; Oudit, G.Y. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. Circ. Res. 2020, 126, 1456–1474.
16. Kuba, K.; Imai, Y.; Rao, S.; Gao, H.; Guo, F.; Guan, B.; Huan, Y.; Yang, P.; Zhang, Y.; Deng, W.; et al. A Crucial Role of Angiotensin Converting Enzyme 2 (ACE2) in SARS Coronavirus-Induced Lung Injury. Nat. Med. 2005, 11, 875–879.
17. Walls, A.C.; Park, Y.-J.; Tortorici, M.A.; Wall, A.; McGuire, A.T.; Veesler, D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell 2020, 181, 281–292.e6.
18. Oudit, G.Y.; Kassiri, Z.; Jiang, C.; Liu, P.P.; Poutanen, S.M.; Penninger, J.M.; Butany, J. SARS-Coronavirus Modulation of Myocardial ACE2 Expression and Inflammation in Patients with SARS. Eur. J. Clin. Investig. 2009, 39, 618–625.
19. Soler, M.J.; Wysocki, J.; Batlle, D. Angiotensin-Converting Enzyme 2 and the Kidney. Exp. Physiol. 2008, 93, 549–556.
20. Zipeto, D.; da Palmeira, J.F.; Argañaraz, G.A.; Argañaraz, E.R. ACE2/ADAM17/TMPRSS2 Interplay May Be the Main Risk Factor for COVID-19. Front. Immunol. 2020, 11, 576745.
21. Ferrario, C.M.; Jessup, J.; Chappell, M.C.; Averill, D.B.; Brosnihan, K.B.; Tallant, E.A.; Diz, D.I.; Gallagher, P.E. Effect of Angiotensin-Converting Enzyme Inhibition and Angiotensin II Receptor

Blockers on Cardiac Angiotensin-Converting Enzyme 2. Circulation 2005, 111, 2605–2610.

22. Eguchi, S.; Kawai, T.; Scalia, R.; Rizzo, V. Understanding Angiotensin II Type 1 Receptor Signaling in Vascular Pathophysiology. Hypertension 2018, 71, 804–810.
23. Imai, Y.; Kuba, K.; Rao, S.; Huan, Y.; Guo, F.; Guan, B.; Yang, P.; Sarao, R.; Wada, T.; Leong-Poi, H.; et al. Angiotensin-Converting Enzyme 2 Protects from Severe Acute Lung Failure. Nature 2005, 436, 112–116.
24. Donoghue, M.; Hsieh, F.; Baronas, E.; Godbout, K.; Gosselin, M.; Stagliano, N.; Donovan, M.; Woolf, B.; Robison, K.; Jeyaseelan, R.; et al. A Novel Angiotensin-Converting Enzyme-Related Carboxypeptidase (ACE2) Converts Angiotensin I to Angiotensin 1-9. Circ. Res. 2000, 87, E1–E9.
25. Mascolo, A.; Scavone, C.; Rafaniello, C.; Ferrajolo, C.; Racagni, G.; Berrino, L.; Paolisso, G.; Rossi, F.; Capuano, A. Renin-Angiotensin System and Coronavirus Disease 2019: A Narrative Review. Front. Cardiovasc. Med. 2020, 7, 143.
26. Ferrario, C.M.; Chappell, M.C. Novel Angiotensin Peptides. Cell. Mol. Life Sci. 2004, 61, 2720–2727.
27. Turner, A.J.; Hiscox, J.A.; Hooper, N.M. ACE2: From Vasopeptidase to SARS Virus Receptor. Trends Pharm. Sci. 2004, 25, 291–294.
28. Vickers, C.; Hales, P.; Kaushik, V.; Dick, L.; Gavin, J.; Tang, J.; Godbout, K.; Parsons, T.; Baronas, E.; Hsieh, F.; et al. Hydrolysis of Biological Peptides by Human Angiotensin-Converting Enzyme-Related Carboxypeptidase. J. Biol. Chem. 2002, 277, 14838–14843.
29. Fischer, M.; Baessler, A.; Schunkert, H. Renin Angiotensin System and Gender Differences in the Cardiovascular System. Cardiovasc. Res. 2002, 53, 672–677.
30. McGuire, B.B.; Watson, R.W.G.; Pérez-Barriocanal, F.; Fitzpatrick, J.M.; Docherty, N.G. Gender Differences in the Renin-Angiotensin and Nitric Oxide Systems: Relevance in the Normal and Diseased Kidney. Kidney Blood Press. Res. 2007, 30, 67–80.
31. Sandberg, K.; Ji, H. Sex and the Renin Angiotensin System: Implications for Gender Differences in the Progression of Kidney Disease. Adv. Ren. Replace 2003, 10, 15–23.
32. Sullivan, J.C. Sex and the Renin-Angiotensin System: Inequality between the Sexes in Response to RAS Stimulation and Inhibition. Am. J. Physiol.-Regul. Integr. Comp. Physiol. 2008, 294, R1220–R1226.
33. Rogers, J.L.; Mitchell, A.R.; Maric, C.; Sandberg, K.; Myers, A.; Mulroney, S.E. Effect of Sex Hormones on Renal Estrogen and Angiotensin Type 1 Receptors in Female and Male Rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2007, 292, R794–R799.
34. Brewster, U.C.; Perazella, M.A. The Renin-Angiotensin-Aldosterone System and the Kidney: Effects on Kidney Disease. Am. J. Med. 2004, 116, 263–272.

35. Touyz, R.M.; Schiffrin, E.L. Signal Transduction Mechanisms Mediating the Physiological and Pathophysiological Actions of Angiotensin II in Vascular Smooth Muscle Cells. Pharm. Rev. 2000, 52, 639–672.
36. Choi, J.; Park, S.; Kwon, T.K.; Sohn, S.I.; Park, K.M.; Kim, J.I. Role of the Histone Deacetylase Inhibitor Valproic Acid in High-Fat Diet-Induced Hypertension via Inhibition of HDAC1/Angiotensin II Axis. Int. J. Obes. 2017, 41, 1702–1709.
37. Rajeshwari, T.; Raja, B.; Manivannan, J.; Silambarasan, T.; Dhanalakshmi, T. Valproic Acid Prevents the Deregulation of Lipid Metabolism and Renal Renin-Angiotensin System in L-NAME Induced Nitric Oxide Deficient Hypertensive Rats. Env. Toxicol. Pharm. 2014, 37, 936–945.
38. Lu, Y.; Yang, S. Angiotensin II Induces Cardiomyocyte Hypertrophy Probably through Histone Deacetylases. Tohoku J. Exp. Med. 2009, 219, 17–23.
39. Struhl, K. Histone Acetylation and Transcriptional Regulatory Mechanisms. Genes Dev. 1998, 12, 599–606.
40. Giannis, D.; Ziogas, I.A.; Gianni, P. Coagulation Disorders in Coronavirus Infected Patients: COVID-19, SARS-CoV-1, MERS-CoV and Lessons from the Past. J. Clin. Virol. 2020, 127, 104362.
41. Klok, F.A.; Kruip, M.J.H.A.; Van der Meer, N.J.M.; Arbous, M.S.; Gommers, D.A.M.P.J.; Kant, K.M.; Endeman, H. Incidence of Thrombotic Complications in Critically Ill ICU Patients with COVID-19. Thromb. Res. 2020, 191, 145–147.
42. Cohen, K.R.; Anderson, D.; Ren, S.; Cook, D.J. Contribution of the Elevated Thrombosis Risk of Males to the Excess Male Mortality Observed in COVID-19: An Observational Study. BMJ Open 2022, 12, e051624.
43. Malas, M.B.; Naazie, I.N.; Elsayed, N.; Mathlouthi, A.; Marmor, R.; Clary, B. Thromboembolism Risk of COVID-19 Is High and Associated with a Higher Risk of Mortality: A Systematic Review and Meta-Analysis. EClinicalMedicine 2020, 29, 100639.
44. Ackermann, M.; Verleden, S.E.; Kuehnel, M.; Haverich, A.; Welte, T.; Laenger, F.; Vanstapel, A.; Werlein, C.; Stark, H.; Tzankov, A.; et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N. Engl. J. Med. 2020, 383, 120–128.
45. Magro, C.; Mulvey, J.J.; Berlin, D.; Nuovo, G.; Salvatore, S.; Harp, J.; Baxter-Stoltzfus, A.; Laurence, J. Complement Associated Microvascular Injury and Thrombosis in the Pathogenesis of Severe COVID-19 Infection: A Report of Five Cases. Transl. Res. 2020, 220, 1–13.
46. Manne, B.K.; Denorme, F.; Middleton, E.A.; Portier, I.; Rowley, J.W.; Stubben, C.; Petrey, A.C.; Tolley, N.D.; Guo, L.; Cody, M.; et al. Platelet Gene Expression and Function in Patients with COVID-19. Blood 2020, 136, 1317–1329.

47. Biembengut, Í.V.; de Souza, T.D.A.C.B. Coagulation Modifiers Targeting SARS-CoV-2 Main Protease Mpro for COVID-19 Treatment: An in Silico Approach. Mem. Inst. Oswaldo Cruz 2020, 115, e200179.
48. Campbell, C.M.; Kahwash, R. Will Complement Inhibition Be the New Target in Treating COVID-19-Related Systemic Thrombosis? Circulation 2020, 141, 1739–1741.
49. Li, T.; Lu, H.; Zhang, W. Clinical Observation and Management of COVID-19 Patients. Emerg. Microbes Infect. 2020, 9, 687–690.
50. Uthman, I.W.; Gharavi, A.E. Viral Infections and Antiphospholipid Antibodies. Semin. Arthritis Rheum. 2002, 31, 256–263.
51. Zhang, Y.; Xiao, M.; Zhang, S.; Xia, P.; Cao, W.; Jiang, W.; Chen, H.; Ding, X.; Zhao, H.; Zhang, H.; et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. N. Engl. J. Med. 2020, 382, e38.
52. Bikdeli, B.; Madhavan, M.V.; Jimenez, D.; Chuich, T.; Dreyfus, I.; Driggin, E.; Nigoghossian, C.D.; Ageno, W.; Madjid, M.; Guo, Y.; et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J. Am. Coll. Cardiol. 2020, 75, 2950–2973.
53. Yang, H.; Xie, W.; Xue, X.; Yang, K.; Ma, J.; Liang, W.; Zhao, Q.; Zhou, Z.; Pei, D.; Ziebuhr, J.; et al. Design of Wide-Spectrum Inhibitors Targeting Coronavirus Main Proteases. PLoS Biol. 2005, 3, e324.
54. Bilaloglu, S.; Aphinyanaphongs, Y.; Jones, S.; Iturrate, E.; Hochman, J.; Berger, J.S. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. JAMA 2020, 324, 799–801.
55. Zhang, L.; Feng, X.; Zhang, D.; Jiang, C.; Mei, H.; Wang, J.; Zhang, C.; Li, H.; Xia, X.; Kong, S.; et al. Deep Vein Thrombosis in Hospitalized Patients With COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. Circulation 2020, 142, 114–128.
56. Gerotziafas, G.T.; Catalano, M.; Colgan, M.-P.; Pecsvarady, Z.; Wautrecht, J.C.; Fazeli, B.; Olinic, D.-M.; Farkas, K.; Elalamy, I.; Falanga, A.; et al. Guidance for the Management of Patients with Vascular Disease or Cardiovascular Risk Factors and COVID-19: Position Paper from VAS-European Independent Foundation in Angiology/Vascular Medicine. Thromb. Haemost. 2020, 120, 1597–1628.
57. Panigada, M.; Bottino, N.; Tagliabue, P.; Grasselli, G.; Novembrino, C.; Chantarangkul, V.; Pesenti, A.; Peyvandi, F.; Tripodi, A. Hypercoagulability of COVID-19 Patients in Intensive Care Unit: A Report of Thromboelastography Findings and Other Parameters of Hemostasis. J. Thromb. Haemost. 2020, 18, 1738–1742.

58. Goshua, G.; Pine, A.B.; Meizlish, M.L.; Chang, C.-H.; Zhang, H.; Bahel, P.; Baluha, A.; Bar, N.; Bona, R.D.; Burns, A.J.; et al. Endotheliopathy in COVID-19-Associated Coagulopathy: Evidence from a Single-Centre, Cross-Sectional Study. Lancet Haematol. 2020, 7, e575–e582.

59. Wang, F.; Hou, H.; Luo, Y.; Tang, G.; Wu, S.; Huang, M.; Liu, W.; Zhu, Y.; Lin, Q.; Mao, L.; et al. The Laboratory Tests and Host Immunity of COVID-19 Patients with Different Severity of Illness. JCI Insight 2020, 5, 137799.

60. Andrianto; Al-Farabi, M.J.; Nugraha, R.A.; Marsudi, B.A.; Azmi, Y. Biomarkers of Endothelial Dysfunction and Outcomes in Coronavirus Disease 2019 (COVID-19) Patients: A Systematic Review and Meta-Analysis. Microvasc. Res. 2021, 138, 104224.

61. Kis, B.; Szupera, Z.; Mezei, Z.; Gecse, A.; Telegdy, G.; Vecsei, L. Valproate Treatment and Platelet Function: The Role of Arachidonate Metabolites. Epilepsia 1999, 40, 307–310.

62. Bishton, M.J.; Harrison, S.J.; Martin, B.P.; McLaughlin, N.; James, C.; Josefsson, E.C.; Henley, K.J.; Kile, B.T.; Prince, H.M.; Johnstone, R.W. Deciphering the Molecular and Biologic Processes That Mediate Histone Deacetylase Inhibitor-Induced Thrombocytopenia. Blood 2011, 117, 3658–3668.

63. Larsson, P.; Alwis, I.; Niego, B.; Sashindranath, M.; Fogelstrand, P.; Wu, M.C.L.; Glise, L.; Magnusson, M.; Daglas, M.; Bergh, N.; et al. Valproic Acid Selectively Increases Vascular Endothelial Tissue-Type Plasminogen Activator Production and Reduces Thrombus Formation in the Mouse. J. Thromb. Haemost. 2016, 14, 2496–2508.

64. Niklas, B.; Idström, J.-P.; Abdoulaye, C.; Hansson, H.; Faijerson-Säljö, J.; Dahlöf, B. A First in Class Treatment for Thrombosis Prevention? A Phase I Study with Cs1, a New Controlled Release Formulation of Sodium Valproate. J. Cardio Vasc. Med. 2019, 5, 1–12.

65. Nasreddine, W.; Beydoun, A. Valproate-Induced Thrombocytopenia: A Prospective Monotherapy Study. Epilepsia 2008, 49, 438–445.

66. Warkentin, T.E.; Sheppard, J.-A.I.; Sigouin, C.S.; Kohlmann, T.; Eichler, P.; Greinacher, A. Gender Imbalance and Risk Factor Interactions in Heparin-Induced Thrombocytopenia. Blood 2006, 108, 2937–2941.

67. Banerjea, M.C.; Diener, W.; Kutschke, G.; Schneble, H.J.; Korinthenberg, R.; Sutor, A.H. Pro- and Anticoagulatory Factors under Sodium Valproate-Therapy in Children. Neuropediatrics 2002, 33, 215–220.

68. Koenig, S.; Gerstner, T.; Keller, A.; Teich, M.; Longin, E.; Dempfle, C.-E. High Incidence of Vaproate-Induced Coagulation Disorders in Children Receiving Valproic Acid: A Prospective Study. Blood Coagul. Fibrinolysis 2008, 19, 375–382.

69. Ugras, M.; Yakinci, C. Protein C, Protein S and Other pro- and Anticoagulant Activities among Epileptic Children Using Sodium Valproate. Brain Dev. 2006, 28, 549–553.

70. Köse, G.; Arhan, E.; Unal, B.; Ozaydin, E.; Guven, A.; Sayli, T.R. Valproate-Associated Coagulopathies in Children during Short-Term Treatment. J. Child Neurol. 2009, 24, 1493–1498.
71. Felisbino, M.B.; Ziemann, M.; Khurana, I.; Okabe, J.; Al-Hasani, K.; Maxwell, S.; Harikrishnan, K.N.; de Oliveira, C.B.M.; Mello, M.L.S.; El-Osta, A. Valproic Acid Influences the Expression of Genes Implicated with Hyperglycaemia-Induced Complement and Coagulation Pathways. Sci. Rep. 2021, 11, 2163.
72. Larsson, P.; Ulfhammer, E.; Magnusson, M.; Bergh, N.; Lunke, S.; El-Osta, A.; Medcalf, R.L.; Svensson, P.-A.; Karlsson, L.; Jern, S. Role of Histone Acetylation in the Stimulatory Effect of Valproic Acid on Vascular Endothelial Tissue-Type Plasminogen Activator Expression. PLoS ONE 2012, 7, e31573.
73. Singh, S.; Singh, K.K. Valproic Acid in Prevention and Treatment of COVID-19. Int. J. Respir. Pulm. Med. 2020, 7, 138.
74. Bambakidis, T.; Dekker, S.E.; Halaweish, I.; Liu, B.; Nikolian, V.C.; Georgoff, P.E.; Piascik, P.; Li, Y.; Sillesen, M.; Alam, H.B. Valproic Acid Modulates Platelet and Coagulation Function Ex Vivo. Blood Coagul. Fibrinolysis 2017, 28, 479–484.
75. Song, W.-C.; FitzGerald, G.A. COVID-19, Microangiopathy, Hemostatic Activation, and Complement. J. Clin. Investig. 2020, 130, 3950–3953.
76. Leatherdale, A.; Stukas, S.; Lei, V.; West, H.E.; Campbell, C.J.; Hoiland, R.L.; Cooper, J.; Wellington, C.L.; Sekhon, M.S.; Pryzdial, E.L.G.; et al. Persistently Elevated Complement Alternative Pathway Biomarkers in COVID-19 Correlate with Hypoxemia and Predict in-Hospital Mortality. Med. Microbiol. Immunol. 2022, 211, 37–48.
77. Afzali, B.; Noris, M.; Lambrecht, B.N.; Kemper, C. The State of Complement in COVID-19. Nat. Rev. Immunol. 2022, 22, 77–84.
78. Gaya da Costa, M.; Poppelaars, F.; van Kooten, C.; Mollnes, T.E.; Tedesco, F.; Würzner, R.; Trouw, L.A.; Truedsson, L.; Daha, M.R.; Roos, A.; et al. Age and Sex-Associated Changes of Complement Activity and Complement Levels in a Healthy Caucasian Population. Front. Immunol. 2018, 9, 2664.
79. Wu, M.; Rowe, J.M.; Fleming, S.D. Complement Initiation Varies by Sex in Intestinal Ischemia Reperfusion Injury. Front. Immunol. 2021, 12, 649882.
80. Kumar, N.; Zuo, Y.; Yalavarthi, S.; Hunker, K.L.; Knight, J.S.; Kanthi, Y.; Obi, A.T.; Ganesh, S.K. SARS-CoV-2 Spike Protein S1-Mediated Endothelial Injury and Pro-Inflammatory State Is Amplified by Dihydrotestosterone and Prevented by Mineralocorticoid Antagonism. Viruses 2021, 13, 2209.
81. Evans, P.C.; Rainger, G.E.; Mason, J.C.; Guzik, T.J.; Osto, E.; Stamataki, Z.; Neil, D.; Hoefer, I.E.; Fragiadaki, M.; Waltenberger, J.; et al. Endothelial Dysfunction in COVID-19: A Position Paper of

the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. Cardiovasc. Res. 2020, 116, 2177–2184.

82. Causey, M.W.; Salgar, S.; Singh, N.; Martin, M.; Stallings, J.D. Valproic Acid Reversed Pathologic Endothelial Cell Gene Expression Profile Associated with Ischemia-Reperfusion Injury in a Swine Hemorrhagic Shock Model. J. Vasc. Surg. 2012, 55, 1096–1103.e51.
83. Chen, L.; Alam, A.; Pac-Soo, A.; Chen, Q.; Shang, Y.; Zhao, H.; Yao, S.; Ma, D. Pretreatment with Valproic Acid Alleviates Pulmonary Fibrosis through Epithelial–Mesenchymal Transition Inhibition in Vitro and in Vivo. Lab. Investig. 2021, 101, 1166–1175.
84. Pastorcic, M.; De, A.; Boyadjieva, N.; Vale, W.; Sarkar, D.K. Reduction in the Expression and Action of Transforming Growth Factor Beta 1 on Lactotropes during Estrogen-Induced Tumorigenesis in the Anterior Pituitary. Cancer Res. 1995, 55, 4892–4898.
85. Van Beneden, K.; Geers, C.; Pauwels, M.; Mannaerts, I.; Verbeelen, D.; van Grunsven, L.A.; Van den Branden, C. Valproic Acid Attenuates Proteinuria and Kidney Injury. J. Am. Soc. Nephrol. 2011, 22, 1863–1875.
86. Wu, C.; Li, A.; Leng, Y.; Li, Y.; Kang, J. Histone Deacetylase Inhibition by Sodium Valproate Regulates Polarization of Macrophage Subsets. DNA Cell Biol. 2012, 31, 592–599.
87. Larsson, P.; Bergh, N.; Lu, E.; Ulfhammer, E.; Magnusson, M.; Wåhlander, K.; Karlsson, L.; Jern, S. Histone Deacetylase Inhibitors Stimulate Tissue-Type Plasminogen Activator Production in Vascular Endothelial Cells. J. Thromb. Thrombolysis 2013, 35, 185–192.
88. Svennerholm, K.; Bergh, N.; Larsson, P.; Jern, S.; Johansson, G.; Biber, B.; Haney, M. Histone Deacetylase Inhibitor Treatment Increases Coronary T-PA Release in a Porcine Ischemia Model. PLoS ONE 2014, 9, e97260.
89. Svennerholm, K.; Haney, M.; Biber, B.; Ulfhammer, E.; Saluveer, O.; Larsson, P.; Omerovic, E.; Jern, S.; Bergh, N. Histone Deacetylase Inhibition Enhances Tissue Plasminogen Activator Release Capacity in Atherosclerotic Man. PLoS ONE 2015, 10, e0121196.
90. Saluveer, O.; Larsson, P.; Ridderstråle, W.; Hrafnkelsdóttir, T.J.; Jern, S.; Bergh, N. Profibrinolytic Effect of the Epigenetic Modifier Valproic Acid in Man. PLoS ONE 2014, 9, e107582.
91. Poli, K.A.; Tofler, G.H.; Larson, M.G.; Evans, J.C.; Sutherland, P.A.; Lipinska, I.; Mittleman, M.A.; Muller, J.E.; D'Agostino, R.B.; Wilson, P.W.; et al. Association of Blood Pressure with Fibrinolytic Potential in the Framingham Offspring Population. Circulation 2000, 101, 264–269.
92. Song, C.; Burgess, S.; Eicher, J.D.; O'Donnell, C.J.; Johnson, A.D. Causal Effect of Plasminogen Activator Inhibitor Type 1 on Coronary Heart Disease. J. Am. Heart Assoc. 2017, 6, e004918.
93. Hrafnkelsdóttir, T.; Ottosson, P.; Gudnason, T.; Samuelsson, O.; Jern, S. Impaired Endothelial Release of Tissue-Type Plasminogen Activator in Patients with Chronic Kidney Disease and

Hypertension. Hypertension 2004, 44, 300–304.

94. Hrafnkelsdóttir, T.; Wall, U.; Jern, C.; Jern, S. Impaired Capacity for Endogenous Fibrinolysis in Essential Hypertension. Lancet 1998, 352, 1597–1598.
95. Newby, D.E.; McLeod, A.L.; Uren, N.G.; Flint, L.; Ludlam, C.A.; Webb, D.J.; Fox, K.A.; Boon, N.A. Impaired Coronary Tissue Plasminogen Activator Release Is Associated with Coronary Atherosclerosis and Cigarette Smoking: Direct Link between Endothelial Dysfunction and Atherothrombosis. Circulation 2001, 103, 1936–1941.
96. Osterlund, B.; Jern, S.; Jern, C.; Seeman-Lodding, H.; Ostman, M.; Johansson, G.; Biber, B. Impaired Myocardial T-PA Release in Patients with Coronary Artery Disease. Acta Anaesthesiol. Scand. 2008, 52, 1375–1384.
97. Van Guilder, G.P.; Hoetzer, G.L.; Smith, D.T.; Irmiger, H.M.; Greiner, J.J.; Stauffer, B.L.; DeSouza, C.A. Endothelial T-PA Release Is Impaired in Overweight and Obese Adults but Can Be Improved with Regular Aerobic Exercise. Am. J. Physiol. Endocrinol. Metab 2005, 289, E807–E813.

Retrieved from https://encyclopedia.pub/entry/history/show/55525