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Mini Review

Mechanism of Blood Vessel Damage in Non-Lethal Influenza Virus Infection in Experimental Animals

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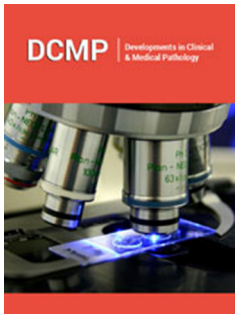

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Introduction

Influenza is an acute respiratory infection that causes significant illness and death in human population. Each year seasonal influenza causes around 1 billion cases, with around 3-5 million cases of severe illness, and 290-650 thousand deaths worldwide [1]. Even though biology of influenza viruses is well studied, pathogenesis of influenza remains the subject of interest of many researchers. Influenza virus predominantly affects epithelia of conductive airway of upper and lower respiratory tract but can also trigger a wide range of complications including disorders in hemostasis and cardiovascular system. The first data indicating the possibility of cardiovascular disorders in patients with influenza were published by clinicians back in the 1950s [2,3]. Thus, influenza can trigger arrhythmias, atrioventricular block, acute myocardial ischemia, myocardial infarction, pericarditis, myocarditis, cardiac tamponade, exacerbation of congestive heart failure, and excess mortality from cardiovascular diseases. It is consistent with epidemiological data on excess mortality during and in the end of influenza epidemics in patients in risk groups with cardiovascular and pulmonary disorder [4].

A wide range of evidence supports a significant role of endothelial dysfunction in pathogenesis of cardiovascular diseases [5]. It has now been established that the vascular endothelium and hemostatic system are targets for the influenza virus. However, this aspect of pathogenesis is currently not taken into consideration in the development of treatment approaches for influenza, and the mechanism by which the virus affects the cardiovascular system remains unknown. This review discusses mechanisms of impairment of pulmonary and mesentery blood vessels in Wistar rats infected with influenza A (H1N1) pdm09 virus. Thus, nonlethal and clinically non-severe influenza infection in rats caused significant impairment of vasomotor activity of blood vessels in different vascular beds [6].

For pulmonary blood vessels of infected rats there was a tendency to increase response to vasodilator with reduce in response to vasoconstrictor, while mesenteric blood vessels had increased response to vasoconstrictor and significant decrease in response to vasodilator. So, the response of pulmonary arteries and mesenteric arteries to vasoconstriction and vasodilator was utterly different, which reflects the physiology of these tissues. Impairment of vasomotor activity of pulmonary and mesenteric blood vessels was found at 24 Hours Post Infection (HPI), as well as at 96hpi, even though viral infectivity titer in pulmonary tissues was significantly reduced at 96hpi (from 6.6 to 2.2lg EID_{50}/ml). Also obtain results indicate a systemic effect of influenza A virus on blood vessels in influenza virus infection.

Influenza A (H1N1) pdm09 virus also causes alteration of endothelial protein expression (eNOS, tPA, PAI-1) in infected endothelial cells (*in vitro*). These endothelial proteins play important role not only in vascular homeostasis and hemostasis, but also in reproduction

of influenza virus infection. Thus, nitric oxide produced by eNOS is potent vasodilator, but also has antiviral, anti-atherogenic, antiproliferative and anticoagulatory effects which maintain vascular homeostasis [7,8]. NO also plays a key role in inflammation: under physiological condition NO has anti-inflammatory effect, while it over production induces inflammation [9]. PAI-1 (serpin E1) is a serine protease synthesized by various cells including endothelial cells. Under normal physio-logical conditions, PAI-1 controls activity of Urokinase Plasminogen Activator (uPA), Tissue Plasminogen Activator (tPA), plasmin and matrix metalloproteinases [10,11]. It is important to notice that infectious activity of influenza A virus can be diminishes by PAI-1, that inhibits cleavage of influenza A virus hemagglutinin [12]. tPA is also a serine protease which converts plasminogen to plasmin needed for dissociation of the fibrin clot. tPA also determine virulence of the influenza virus, since plasmin (released from plasminogen by its cleavage by tPA) is one of the main enzymes that cleave influenza virus hemagglutinin (HA0 to HA1 and HA2) which increases virus infectivity [13].

Expression of these endothelial proteins was studied in the EA. hy926 human endothelial cell line infected with influenza A (H1N1) pdm09 virus. Thus, expression of eNOS was significant decrease at 6, 12, 18, 24, 48 and 72hpi, while expression of PAI-1 and tPA was modulated over the course of experiment [14]. Obtain results indicate development of influenza induced endothelial dysfunction. How influenza A (H1N1) pdm09 virus can alter functional activity of endothelial cells including vasomotor activity and expression of endothelial proteins? One of possible answer can be molecular mimicry between viral and cellular proteins. Additional studies reveled that almost all proteins of influenza viruses have fragments with high degree of homology to fragments of cellular proteins, including eNOS, tPA, PAI-1 [15]. Virus can regulate endothelial proteins expression in two ways:

A. By direct regulation of homologous fragment after proteolysis of viral protein.

B. By inducing autoantibody to this homologous fragment.

The possibility of such a variant of the pathogenesis of autoimmunity is confirmed by the results of vaccination against the 2009-2010 influenza pandemic. Vaccination with the Pandemrix vaccine (GlaxoSmithKline) has resulted in a sharp increase in the incidence of narcolepsy in children and adolescents in different countries. Comparison of the characteristics of different vaccines showed the existence of a connection be-tween the occurrence of narcolepsy and the high content of the influenza virus nucleoprotein in the Pandemrix vaccine and antibody formation to it that cross-reacted with the hypocretin (orexin) receptor 2. As it turned out, the hypocretin 2 receptor contains a motif in its extracellular loop, presented also in nucleoprotein [16]. Obtained results indicate that influenza A (H1N1) pdm09 virus causes endothelial dys-function in that non-lethal and clinically non-severe experimental influenza virus infection in experimental animals. In addition, our result can serve as a basis for expanding the influenza therapy and including medications with endothelial and vaso protective effect in treatment regimens. Probably this recommendation is more relevant for patients with cardiovascular diseases. Increased attention should also be paid to the safety of influenza vaccines in terms of their possible effects on blood vessels. This is especially important in the light of recent publications on the blood vessels damage after vaccination against COVID-19 [17,18].

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