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A possible method of inhibition of virus COVID-19 reproduction through induction of intra-cellular synthesis and upregulation of interferon I

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The article substantiates studies on the inhibition of virus COVID-19 reproduction within the organism based on upregulation of intracellular interferon I through strengthening synthesis and upregulation of heat shock protein with the molecular mass of 70 kDa.

Keywords: *Virus COVID-19, heat shock protein 70 kDa, intra-cellular interferon upregulation*

Infectious disease, caused by virus COVID-19 and initiated in Wuhan region of China, presently has been spread over more than 200 countries worldwide. Owing to high level of dissemination of virus COVID-19 World Health Organization declared pandemic situation. Naturally, scientists all over the world currently are applying their efforts and modern techniques to elaborate therapy of virus COVID-19.

As it is known from scientific literature, in contrast to the Chinese species, the species of virus COVID-19, widely spread in Europe, are subjected to high level of mutagenicity (Pachetti et al., 2020). On the other hand, significant body of anticipated treatment methods is predominantly related to immunological approaches. In particular, utilization of immunoglobulins to virus COVID-19 provided from the serum of recovalescent patients in therapeutic purposes (passive immunization) or vaccination with virus COVID-19 (active immunization) are based on and utilize antigen-antibody reaction requiring high specificity and mutual recognition between participating agents. Hence, taking into account high level of mutagenicity of European species of virus COVID-19, one can come to a conclusion that in choosing therapy methods of the patients infected with this virus, along with immunological methods application of other methods is important.

Mammalian organisms possess very strong intrinsic protective system and heat shock proteins belong to this system. Being at low levels at normal conditions, under exposure of the organism to adverse factors of different origin immediate (within 3-4 h) launching of synthesis of heat shock proteins is noticed. The results of the studies carried out on different species of animals show that induction of synthesis and upregulation of heat shock proteins having molecular mass of 70 kDa (HSP70) in the tissues is capable of protecting the organism from such severe infectious disease as peritonitis (Allahverdiyeva et al., 2019). At the same time upregulation of HSP70 makes possible to protect somatic cells of the organism from the most part of mutagenic changes induced by damaging impact of high doses of polyaromatic hydrocarbons, poisonous phenol, heavy metals and neonicotinoid insecticides (Mekhtiev and Movsum-zadeh, 2008; Mustafayev and Mekhtiev, 2014; Mekhtiev et al., 2017). HSP70 have enough potency not only in protecting somatic cells from impact of adverse factors in preventive way, but as well in recovery of the already damaged tertiary and secondary structures of denaturized proteins (Ismailova and Mekhtiev, 2018).

As it is known from literature, HSP70 are potent in strengthening intra-cellular synthesis of interferon (Jacquemin et al., 2017). In particular, HSP70 binds specifically to Toll-like receptors 4 (TLR4; Kono and Rock, 2008). TLRs 2 and 4 were originally known as receptors recognizing patho-

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gen-associated molecular patterns, but subsequently it was recognized that TLRs as well are capable of binding to endogenous ligands including HSP molecules (Vabulas et al., 2002). Traumatic brain injury results in high level expression of TLR4 and HSP70 in macrophages/microglia and astrocytes revealed with immunohistochemistry technique. Interestingly, HSP70 was expressed not only in macrophage/microglia and astrocytes but also in neurons, such that injury of any cell type (glia or neurons) could release HSP70 that finally brought to TLR4 signaling (Zhang et al., 2012). Furthermore, ligand-mediated activation of TLR4 also triggers signal transduction for the induction of type I interferon (Kawai and Akira, 2010). Along with the above said, it has been shown in the studies that, in contrast to SARC-1 virus, strengthening of interferon I synthesis bringing to its intracellular upregulation, realizes damaging effect on COVID-19 virus (Vanderheiden et al., 2020; Mantlo et al., 2020; Fig. 1).

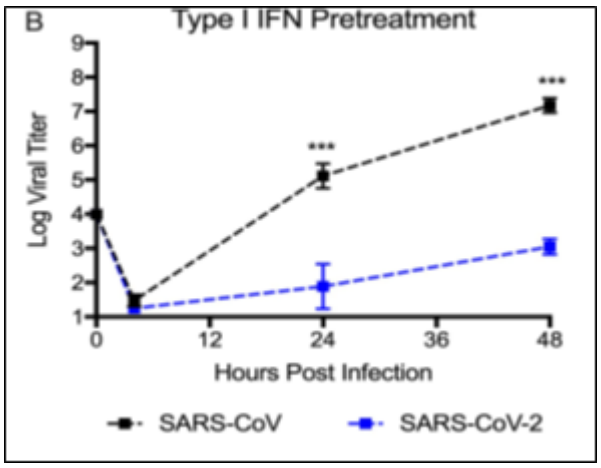

Fig. 1. Sensitivity of COVID-19 virus to type I IFN pretreatment. Vero E6 cells were treated with 1000 units of recombinant type I IFN or mock for 18 hours prior to infection. Cells were subsequently infected at with either SARS-CoV WT (black) or COVID-19 (blue) at an MOI of 1. Each point (n=6) on the line represents the group mean. The two tailed Students t-test: *** - $p<0.001$ (Kumari et al., 2020).

Taking into account the presented data on a whole, one can come to a conclusion that upregulation of HSP70 in the cells of the patients, infected with COVID-19 virus, will make possible realization of effective struggle with it.

In the Academician Abdulla Garayev Institute of Physiology serotonin-modulating anticonsolidation protein was identified first in the rat brain cortex and thereafter purified from the whole brains of the rats and cows (Mekhtiev, 2000). This protein is in linear relation with neurotransmitter serotonin and can realize its functions on sub-cellular level. The studies carried out earlier in our Department on different conditioned models with positive and negative reinforcements, showed that intra-cerebral administration of SMAP to the animals prior to learning sessions brings to significant impairment in memory formation (Mekhtiev, 2000; Guseinov, Mekhtiev, 2013). At the same time the results of our other earlier studies with application of highly sensitive immunochemical Western blotting and ELISA-test techniques showed that within three-hour timeframe from systemic administration of SMAP into the organisms of different animal species, sharp upregulation of HSP70 in their tissues (liver, retina) is observed (Ismailova and Mekhtiev, 2018; Allahverdiyeva et al., 2019).

The studies carried out in our Department demonstrated that upregulation of HSP70 in peripheral tissues can be achieved not only through systemic, but as well through intra-cerebral administration of SMAP to animals. In particular, in the studies conducted over sazan specimens, SMAP administration into the fourth brain ventricle within 4 h brought to significant up-regulation of HSP70 in the liver and back muscles, revealed with ELISA-test ($p<0.001$; Fig. 2).

The said results can be explained in the light of the discovery of peripheral serotonergic nervous system by Prof. V.Smirnov and his colleagues in 2015 y., confirmed by other researchers abroad. According to the results of his pioneer studies, along with sympathetic and parasympathetic nervous systems, peripheral serotonergic nervous system, penetrating all peripheral tissues of the organism, as well exists (Smirnov et al,, 2015). Hence, basing on his data, one can conclude that signal appeared in the brain serotonergic system, via peripheral serotonergic nervous system is delivered to peripheral tissues. At the same time, as other authors have shown, medicine can be delivered directly to the brain (missing blood circulation) through their intra-nasal administration (Pardeshi et al., 2013). After the administration of preparations into the nasal cavity, they reach brain structures within 30-40 min without any loss.

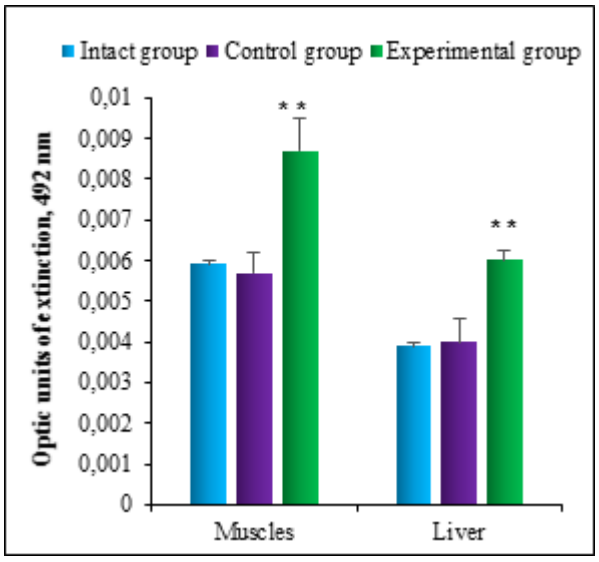

Fig. 2. Effect of administration of SMAP into IV brain ventricle on HSP70 level in the dorsal muscles and liver of sazan specimens. ** - p<0.01.

Concluding the presented data, one can come to an idea that in combatting COVID-19 virus for the purpose of strengthening interferon synthesis and its upregulation inside the cells of the infected patients, it is reasonable and possible to utilize intra-nasal administration of SMAP to the infected patients providing its direct delivery into the brain structures and thereafter upregulation of HSP70 in the peripheral tissues through peripheral serotonergic nervous system.

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İnterferon I-nin hüceyrədaxili sintezinin güclənməsi və miqdarının artırılması vasitəsilə COVID-19 virusunun inhibə etməsinə dair güman olunan üsul

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Məqalədə 70 kDa istilik şoku zülallarının sintezinin gücləndirilməsi və miqdarının artırılması vasitəsilə hüceyrədaxili səviyyədə interferon I miqdarının artırılması əsasında orqanizm daxilində COVID-19 virusunun reproduksiyasının inhibə edilməsi aparılacaq tədqiqatları əsaslandırır.

Açar sözlər: *Virus COVID-19, 70 kDa istilik şoku zülalı, hüceyrədaxili interferon I səviyyəsinin artırılması*

Возможный способ ингибирования репродукции вируса COVID-19 посредством усиления синтеза и увеличения внутриклеточного уровня интерферона I

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В статье приводятся аргументы в пользу проведения исследований по ингибированию репродукции вируса COVID-19 в организме, основанному на повышении внутриклеточного уровня интерферона I посредством усиления синтеза и повышения уровня белков теплового шока с молекулярной массой 70 кДа.

Ключевые слова: *Вирус COVID-19, белки теплового шока с молекулярной массой 70 кДа, повышение уровня внутриклеточного интерферона I*