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The α7 Nicotinic Acetylcholine Receptor: a Key Molecule in Post-COVID Syndrome?

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Abstract

Post Acute Sequelae of COVID-19 (PASC) appears with a considerable delay after recovery from the acute phase and lasts for months or even years. It includes injuries of multiple organs, as well as cognitive impairment, fatigue, disordered sleep and memory loss. In spite of substantial efforts undertaken to understand the nature of this pathology the mechanisms of its development remain unclear and no efficient treatment has been suggested. The present review provides evidence indicating the important role of α7 nicotinic acetylcholine receptors in COVID19 pathogenesis and PASC development and suggests the involvement of immune mechanisms stimulated by SARS-Cov-2 S-protein fragment 674-685 possessing homology with α7-specific ligands. It is hypothesized that delayed PASC symptoms can be stimulated by α7-specific antibodies of anti-idiotypic origin; consequently, the therapeutic approaches to cure or prevent PASC development should include measures to both neutralize such antibodies and additionally stimulate α7 nicotinic acetylcholine receptors.

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COVID-19 has taken millions of lives throughout the world since 2019. The quarantine measures and anti-virus vaccines allowed slowing the spread of infection. However, people who have recovered from the acute disease often continue to suffer from its consequences. This state was called Post Acute Sequelae of COVID-19 (PASC), “post-COVID” or “long COVID”. The PASC is a debilitating state which appears after the acute phase cessation, sometimes with a considerable delay of weeks or even months after recovery, and lasts for months or even years. It is a multi-organ pathology including injuries of heart, lungs, kidney, liver, spleen, pancreas, gastrointestinal tract, as well as cognitive impairment, fatigue, disordered sleep and memory loss (reviewed in Davis et al., 2023). In spite of substantial efforts undertaken to understand the nature of this pathology the mechanisms of its development remain unclear and no efficient treatment has been suggested. The present review provides evidence indicating the important role of cholinergic mechanisms, in particular, those mediated by α7 nicotinic acetylcholine receptors (α7 nAChRs), the mechanisms of their impairment in PASC pathogenesis and suggests the ways of treatment.

The α7 nAChRs belong to the family of nAChRs. The members of this family were at first characterized as ligand-gated ion channels mediating fast synaptic transmission in neuro-muscular junctions and autonomic ganglia (Lindstrom, 1996). Further, it was discovered that nAChRs are also present in many non-excitable cells and are involved in regulating cell survival, adhesion and proliferation, as well as neurotransmitter and cytokine release (reviewed in Skok, 2022a). Structurally, they are pentameric transmembrane proteins composed of 10 types of α subunits (α1 to α10) and 4 types of β subunits (β1 to β4) combined in several established combinations. The muscle nAChRs contain γ, ö and ε subunits in addition to α1 and β1 subunits. (Lindstrom, 1996). The autonomic ganglia contain mainly α3(α5)β4 nAChRs, while α4β2 nAChRs are mainly expressed in the brain (Gotti et al., 2009). The nAChRs composed of α7 subunits, either as homopentamers, or heteropentamers with β2 subunits, are the most ubiquitous: they are found in the brain and autonomic ganglia and in many, if not all, non-excitable cells; they were also found in mitochondria and cell nuclei outer membranes (Kawashima et al., 2015; Skok, 2022b; Kalashnyk et al., 2023). They can function/signal both ionotropically and metabotropically; however, their ion channel is quickly desensitized; therefore, most probably, their functions are mainly mediated in ion-independent manner, through conformational/allosteric movements affecting neighboring receptors and signaling molecules (King et al., 2015).

One of the most widely studied functions of α7 nAChRs is their ability to control the release of pro-inflammatory cytokines by the cells of monocyte origin and in such a way to attenuate inflammation (De Jonge and Ulloa, 2007). Acetylcholine released from the vagus nerve endings was shown to affect α7 nAChRs on peritoneal macrophages (Wang et al., 2003). The classical symptom of COVID-19 is hyperinflammation caused by excessive release of pro-inflammatory cytokines (the “cytokine storm”). Therefore, the α7 nAChRs, known to be involved in regulating inflammation, appeared in the center of attention. SARS-Cov-2 infection was found to be accompanied by vagus nerve neuropathy (Moyano et al, 2021) and impaired vagal activity was found in long-Covid patients (Acanfora et al., 2022). It was suggested that SARS-CoV-2 induces vagus nerve inflammation followed by autonomic dysfunction which contributes to critical disease courses and might contribute to dysautonomia observed in long COVID (Woo et al., 2023). Cholinergic disfunction upon COVID-19 has already been discussed (Nadwa et al., 2023).

The α7 nAChRs were also shown to control neuroinflammation in the brain and in such a way influence learning and memory. In our experiments, mice treated with bacterial lipopolysaccharide (LPS) developed neuroinflammation and demonstrated decreased levels of α7 nAChRs in the brain and impaired episodic memory (Lykhmus et al.,2015). Injections of α7-selective agonist PNU282987 prevented both α7 nAChR decrease and memory decline under the effect of LPS (Lykhmus et al., 2020). Neuroinflammation is considered to accompany and even provoke neurodegeneration in Alzheimer and Parkinson diseases (Onyango et al., 2021). In our experiments, injections of PNU282987 improved memory of transgenic APP43PS1 mice, an established model of Alzheimer disease (Lykhmus et al., in preparation). COVID-19 neuropathology was shown to include Alzheimer-like features (Reiken et al., 2022). COVID-19 patients seem to be more prone to developing Alzheimer disease and Alzheimer patients could be more susceptible to severe COVID-19 (Ciassio et al., 2021). The brain metabolite kynurenic acid inhibits α7 nicotinic receptor activity (Hilmas e al., 2001). Activation of the kynurenine pathway has been identified in long COVID, and is associated with cognitive impairment (Cysique et al., 2022).

The data provided above clearly indicate that SARS-Cov-2 infection affects α7 nAChRs. The mechanism of such influence was first suggested in the paper of Changeux et al, 2020, where it was shown that the fragment 674-685 of SARS-Cov-2 spike protein possesses structural homology with known ligands of α7 nAChRs: α-cobratoxin, α-bungarotoxin and rabies virus; the latter penetrates infected cells through α7 nAChR. Structural studies confirmed this idea and showed that peptide Y674-R685 penetrates deeply into the binding pocket of α7 nAChR and forms interactions with aromatic residues of adjacent loops B and C (Oliveira et al., 2021). Electrophysiological experiments demonstrated that this peptide exerts a dual effect on α7. It activates α7 nAChRs in the presence of positive allosteric modulators but decreases the α7 channel activity elicited by acetylcholine (Chrestia et al., 2022), possibly, because of the competition for acetylcholine-binding site. In our experiments, peptide 674-685 competed with α7-specific antibodies for the binding to α7(179-190) fragment and attenuated cytochrome *c* release from mitochondria stimulated with Ca^{2+} similarly to other α7-selective ligands including α7-binding fragment of α-cobratoxin (Kalashnyk et al., 2021). We suggested that when the virus penetrates the infected cell and its protein part is cleaved by cellular proteases, fragment 674-685 can influence mitochondria and support the cell viability during the period necessary for virus replication by inhibiting mitochondria apoptosis pathway.

Fragment 674-685 contains a PRRA motif, a four-residue insertion not found in other SARS-like coronaviruses (Oliveira et al., 2021). This positively charged cluster of amino acids can mimic the quaternary nitrogen of choline underlying the SARS(674-685) interaction with α7 nAChR. This fragment is naked upon the virus spike protein cleavage by cellular protease and is considered important for the binding to neuropilin that favors the virus penetration into the cell (Abebe et al., 2021). The main gate for the SARS-Cov-2 entry into the cell is considered to be angiotensin-converting enzyme-2 (ACE-2) receptor (Wang et al.,2020). We have found that ACE-2 expressed in astrocytoma U373 cells interacts with α7 nAChR because their complex was identified in U373 cell lysates by Sandwich ELISA (Lykhmus et al., submitted). Therefore, affecting α7 nAChR can interfere with (prevent) virus penetration into the cell. However, this idea needs experimental confirmation.

Interestingly, SARS(674-685) peptide was shown to interact not only with α7 nAChRs, but also with α4β2 and muscle (α1β1γö) nAChR subtypes; however, the mode of binding was somehow different from that with α7 nAChR and was similar to the binding of antagonists (Oliveira et al., 2021). Possibly this finding can explain why COVID-19 infection increases the risk of new-onset myasthenia gravis, a disease affecting muscular nAChRs (Tugasworo et al., 2022).

Another line of evidence demonstrates that SARS-Cov-2 S-protein possesses one more site capable to bind nAChRs, namely fragment 381-386, also with homology to a sequence of a snake venom toxin (Farsalinos et al., 2020; Lagoumintzis et al., 2021).

The data on direct interaction of SARS-Cov-2 with nAChRs allowed hypothesizing that nicotine and other cholinergic agonists can have a protective role. The data on the role of smoking upon COVID-19 are contradictory: some of them indicate that smoking people are rare among patients with severe COVID; others show that smoking aggravates the infection (Shastri et al., 2021). However, adding AChE inhibitor to the treatment protocol (that increases the level of acetylcholine and stimulates nAChR activation) is beneficial (Foster et al., 2023). We have found that another re-purposed

drug, hydroxyurea, which appeared to be very efficient in treating patients with severe COVID (Foster et al., 2021), can bind α7 nAChR and, in fact, behaves as a positive allosteric modulator of this nAChR subtype (Lykhmus et al., submitted).

Taken together, the data presented clearly demonstrate that α7 nAChRs are involved in pathogenesis of COVID-19 and that SARS-Cov-2 can directly affect this nAChR subtype. Such interaction can influence both virus penetration into the cell and the inflammatory process stimulated by infection. Therefore, stimulating α7 nAChRs by either endogenous acetylcholine or externally added agonist/allosteric modulator can be beneficial for treatment of COVID patients. However, the situation with post-COVID syndrome (PASC) is not so clear. This state develops weeks or even months after recovery from the acute phase of infection and is hardly to be explained by continuous virus persistence in the organism. On the other hand, such a delay indicates that certain immunological mechanisms, which develop slowly, can be involved.

We immunized mice with SARS(674-685) peptide and observed an inflammatory response and a dramatic decrease of their episodic memory, which could be prevented by injections of choline, an α7 nAChR agonist. The brains of immunized mice contained decreased amounts of α7 nAChR compared to those of non-immunized mice; choline injections restored them to normal levels and hydroxyurea injections decreased IL-1β levels in the brain (Lykhmus et al., 2022 and submitted). Memory loss could be transferred to non-immunized mice by injections of immunoglobulins purified from the blood sera of immunized mice (Lykhmus et al., 2022). Analysis of these immunoglobulins demonstrated that they contain SARS(674-685)-specific antibodies (both IgM and IgG), as well as α7(179-190)-specific antibodies (mainly IgM) (Lykhmus et al., 2022 and submitted). The α7(179-190)-specific antibodies were previously shown to cause inflammatory reaction, to decrease α7 nAChR content in the brain and to impair memory (Lykhmus et al., 2015). Therefore, these are α7(179-190)-specific antibodies which could be a pathogenic factor causing memory loss in SARS(674-685)-immunized mice. The working hypothesis to explain the appearance of α7(179-190)-specific antibodies in SARS(674-685)-immunized mice is the involvement of idiotype-anti-idiotype network. Anti-idiotypic antibodies are regarded as “internal image” of the antigen stimulating primary (idiotypic) antibody production (Jerne and Cocteau, 1984). In our case, the antigen is SARS(674-685), which binds to α7(179-190); therefore, anti-idiotypic antibody should also bind α7(179-190) that is actually observed. Anti-idiotypic antibodies are produced in response to idiotypic ones; therefore, their appearance is delayed compared to primary idiotypes. Indeed, we observed IgM anti-α7(179-190) after second immunization with SARS(674-685) when both IgM and IgG anti-SARS(674-685) were already present in the blood. The α7-specific anti-idiotypic antibodies can explain the pathogenic symptoms of PASC, which appear quite long after the acute phase of COVID.

Auto-anti-idiotypic antibodies are generated during anti-viral immune response (Jiang et al., 2003; Tzioufas and Routsias, 2010) that supports our hypothesis. Moreover, anti-idiotypic vaccines for a number of viruses including reovirus, rabies virus, murine mammary tumor virus (MMTV), murine leukemia virus, hepatitis B virus (HBV) and human immunodeficiency virus (HIV) have been developed (Naveed et al, 2018).

We found both SARS(674-685)-specific and α7(179-190)-specific antibodies in the blood of people who experienced COVID-19 two to six months ago; many of them complained for the cognitive impairment including memory loss.

The α7 nAChRs are expressed in many organs and tissues. Therefore, the presence of anti-idiotypic α7-specific antibodies can explain multi-organ symptoms of PASC. In contrast to the live virus, such antibodies can persist for a long

time; moreover, their generation is stimulated by SARS(674-685)-specific antibodies. In fact, this is a self-supporting system where idiotypic and anti-idiotypic antibodies stimulate each other; as a result pathogenic consequences of their interaction with cells and tissues can persist for a long time that is actually observed.

Assuming that α7 nAChRs are the key targets for pathogenic antibodies, the most evident therapeutic solution to overcome their influence is the use of α7-selective agonists, which stimulate α7 nAChR signaling and can prevent α7(179-190)-specific antibody binding (because α7(179-190) fragment contains the elements of agonist binding site). AChE inhibitors can also help by increasing the endogenous acetylcholine levels. The less evident and advanced solution may be the injections of protein-conjugated α7(179-190), which should neutralize α7(179-190)-specific antibodies and favor their elimination that can both prevent their pathogenic effects in cells and interrupt the idiotype-anti-idiotype loop.

In conclusion, the available data indicate that (1) α7 nAChRs play a key role in COVID19 pathogenesis and PASC development; (2) PASC symptoms can be stimulated by α7-specific antibodies of anti-idiotypic origin; and (3) the therapeutic approaches to cure or prevent PASC development should include measures to both neutralize such antibodies and additionally stimulate α7 nAChRs.

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