Attenuated Effect of Rivastigmine on IL-1 β IL-6, and TNF-α Level in LPS-Induced cytokine storm in Mice

Rivastigmine is a carbamate cholinesterase inhibitor (ChEI) with a pseudo-irreversible activity that can inhibit not only acetylcholinesterase (AChE) but also butyrylcholinesterase (BuChE) [16, 17]. Oral administration of Rivastigmine was approved by the US Food and Drug Administration (FDA) in 2000 for the treatment of Alzheimer's disease (AD) [18] Mild to moderate Alzheimer's disease was treated and improved by Rivastigmine. Our study showed that Rivastigmine 0.5 mg/kg (Shifrin, et al. 2013) highly significantly decreased pro-inflammatory cytokine secretion (IL-1β, IL-6, and TNF-α) P< 0.001 as compared to the LPS group, that's was consistent with the previous study showing that Galantamine which is an acetylcholine esterase enzyme inhibitor suppressed the expressions of TNF-α, IL-1β, and IL-6 in the lungs, this suggests that Galantamine suppressed acute inflammatory response during the cholinergic anti-inflammatory pathway of acute acid aspiration-induced ARDS, and also suppressed the inflammation mediator HMGB1 [19]. In previous studies was shown ACh was inhibit pro-inflammatory cytokine production by activated macrophages.

Murine macrophages were activated by lipopolysaccharide (LPS), an endotoxin produced by all gram-negative bacteria and implicated in the pathogenesis of septic shock [20], to secrete TNF-a, IL-1b, and IL-6, all pro-inflammatory cytokines. ACh at the micromolar range significantly reduced this cytokine secretion [21], So the use of Rivastigmine as an AChE inhibitor that decreases the expression of NF-κB by activating α7 nicotinic acetylcholine receptors (α7nAChR) was involved in the anti-inflammatory effect of the cholinergic anti-inflammatory pathway [22]. This pathway inhibited the excessive production of TNF-α, IL-1β, and IL-6 mediated by the nicotinic acetylcholine receptor (nAChR) α7 subunit on macrophages [23, 24]. Mice deficient of the α7 subunit exhibited increased endotoxin-induced TNF production, which explains the role of α7 nAChRs in the inflammatory pathway [25, 26]. Macrophages appear to be very sensitive to acetylcholine, which suggests that any source of acetylcholine, even from non-neuronal sources such as epithelial and endothelial cells [26, 27], could also modulate the activity of adjacent macrophages [28]. Besides TNF, other pro-inflammatory cytokines are inhibited by acetylcholine, such as high mobility group B1 (HMGB1), IL-1β, and IL-6. The treatment of Rivastigmine can increase the antioxidant capacity, increase glutathione reductase and homocysteine, and that's important to reduce the peroxidation product MDA and the inflammatory mediator IL-6 [29, 30].

Effects of Rivastigmine on Lung Fibrosis

Enhancement of parasympathetic domination leads to inhibition of proinflammatory cytokine release and attenuation of tissue lung injury, that's mediated by cholinergic activation via Rivastigmine which downregulates acetylcholinesterase (AChE) improves autonomic influence and reduces inflammatory reactions [31, 32].

Rivastigmine has pleiotropic pharmacological effects through its antioxidant, anti-inflammatory, and anti-apoptotic roles. Our results showed that Rivastigmine significantly less inflammation and distortion of pulmonary architecture, mild congestion, obvious decreasing thickness in the interalveolar septae, and slightly inflammatory cell infiltration (1-33) % (highly significant differences P<0.001) in comparison with LPS-induced group [33]. This effect was mediated through the preserving Ach, which stimulated the nicotinic receptor α7nAChR in the macrophages and reduced the cytokine storm of the macrophages. These results were consistent with a previous study that revealed the important role of the cholinergic anti-inflammatory pathway and activation of α7nAChR as anti-inflammatory effects by inhibiting the release of pro-inflammatory cytokines [34].

Therefore, cholinergic receptors mainly α7nAChR, and related cholinergic agonists like Rivastigmine may affect the pathogenesis of SARS-CoV-2 infection. Cholinergic dysfunction in COVID-19 is due to dysregulation of α7nAChR by SARS-CoV-2 promoting the central sympathetic drive with the development of the sympathetic storm. As well, α7nAChR activators through interaction with diverse signaling pathways can reduce the risk of inflammatory disorders of cytokine storm in COVID-19[35, 36]. In addition, α7nAChR activators may mitigate endothelial dysfunction, oxidative stress, and associated coagulopathy in a cytokine storm. Therefore, α7nAChR activators like Rivastigmine in virtue of its anti-inflammatory and anti-oxidant effects with direct anti-SARS-CoV-2 effect could be effective in the management of cytokine storm in COVID-19 [37, 38].

CONCLUSION

A dose of 0.5 mg/kg of Rivastigmine and its combination with methylprednisolone showed obvious therapeutic effects on cytokine storm induced by LPS in Swiss Albino mice by highly significantly reducing the proinflammatory cytokines IL-1, IL-6, TNF-, and TGF- levels and subsequently protecting the tissue of lungs from damage. Half doses of both Rivastigmine plus Methylprednisolone (RAMP) showed no obvious advantage in comparison with Rivastigmine (RA) alone in induced cytokine storm in mice.

Rivastigmine dramatically suppressed and decrease lung fibrosis by inhibiting and controlling the expression of TGF-β and reducing exudative DAD, desquamation of hyperplastic pneumocystis, fibrosis, and squamous metaplasia in mice with LPS-induced cytokine storm, as seen in the current study. It has the potential to one-day serve as a helpful treatment for ARDS and other forms

of acute lung injury.

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