Targeting cAMP-specific phosphodiesterase to treat acute respiratory distress syndrome

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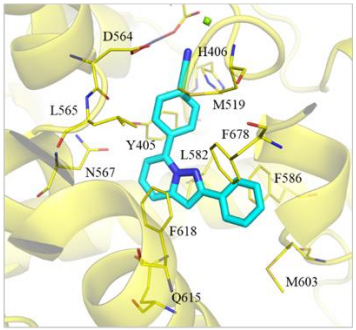

Introduction. Neutrophils play a critical role in developing acute respiratory distress syndrome (ARDS) by migrating to the lungs and releasing inflammatory mediators.

Aims. To investigate the anti-inflammatory effects and underlying mechanisms of 4-(2-phenylpyrazolo[1,5-a]pyridin-7-yl)benzonitrile (WHC14) in reducing neutrophil activity and its potential therapeutic efficacy in ARDS.

Methods. Human neutrophils were used to determine the effects of WHC-14 on respiratory bursts and degranulation, and to study the underlying molecular mechanisms. In silico analyses and enzymatic activities were performed to determine the inhibitory effects of WHC-14 on PDE activities. In the in vivo studies, ARDS was induced in mice using an intratracheal administration of lipopolysaccharide (LPS).

Results. WHC14 significantly inhibited the production of superoxide anion and the generation of reactive oxygen species (ROS) in activated human neutrophils. However, it only showed minor inhibition of elastase release. WHC14 increased the intracellular levels of cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) activity in activated neutrophils. The anti-inflammatory effects of WHC14 on superoxide anion production, ROS generation, and elastase release were significantly reversed by PKA inhibitors. Enzyme assays and molecular docking studies indicated that WHC14 is a non-selective inhibitor of PDEs. In the mouse model of LPS-induced ARDS, WHC14 treatment mitigated lung damage and reduced neutrophil infiltration, oxidative stress, and IL-1β levels.

Discussion. These results indicate that WHC14 acts as a PDE inhibitor and effectively suppresses neutrophil inflammatory responses by activating the cAMP/PKA pathway. These findings highlight the potential of WHC14 as a promising drug lead for the treatment of ARDS.