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Nisoldipine Intervene with the Virus Incorporation Procedures to Block Viral Infection in Cells and *In Vivo*

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Introduction

The Influenza A Virus (IAV) is a major pathogen that can cause epidemics and global pandemics in humans and other animal species. As a result, a large number of cases occur globally each year, posing a serious threat to human health. The World Health Organization (WHO) estimates that the annual influenza epidemic causes 3 to 5 million cases of severe illness and 290,000 to 650,000 respiratory deaths. Vaccination is widely regarded as the most effective method of protecting both human and animal populations from epidemic influenza, but vaccines must be constantly updated to account for the emergence of new circulating strains. Aside from the development of effective vaccines, anti-influenza agents are an important alternative therapy for both influenza prevention and treatment. There are currently only three types of M2 ion channel, neuraminidase, and viral RNA polymerase inhibitors are among the antiviral drugs approved for use against influenza. M2 inhibitors (amantadine and rimantadine) are, however, no longer used due to widespread resistance and severe side effects. As a result, neuraminidase (NA) inhibitors (oseltamivir, zanamivir, peramivir, and laninamivir) and a polymerase acidic protein (PA) inhibitor (baloxavir marboxil) have emerged as antiviral treatment mainstays. However, due to IAV's high mutagenic capacity, the virus's increasing resistance to NA and PA inhibitors is cause for concern. Although some novel drugs, such as pimodivir, have been developed, the antiviral options for influenza remain limited. As a result, new antiviral approaches to combating influenza are required. With a particular emphasis on virus-host cell interactions [1].

Description

Target Molecule Corp. provided 98% pure nisoldipine (T0163), cilnidipine (T0388), nitrendipine (T0119), nimodipine (T0343), and methyl—cyclodextrin (MCD, T4072). Solarbio supplied chlorpromazine hydrochloride (CPZ, C7010). Macklin provided ammonium chloride (A801304). Sigma-Aldrich provided EGTA, BAPTA-AM (1,2-bis (o-aminophenoxy) ethane-N, N, N′, N′-tetraacetic acid acetoxymethyl ester) and zanamivir. In our laboratory, we synthesised CL-385319 and D715-2441 with 98% purity. Invitrogen provided Alexa 568 conjugated human transferrin (Tf-568, T23365). Absin provided FITC-conjugated cholera toxin beta subunit (CTB-FITC, abs80003). The following antibodies were used: influenza A virus PB2 protein antibody (Genetex, GTX125926); influenza A virus NP antibody (Genetex, GTX125989); mouse anti-transferrin antibody (Bioss, bsm-33244M); and influenza A virus NP antibody (Genetex, GTX125989) [2].

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Anti-caveolin-1 rabbit mAb (Bioss, bs-1453R); anti-Cav1.2 rabbit mAb (Abcam, ab84814); and GAPDH (glyceraldehyde-3-phosphate dehydrogenase)/-actin rabbit mAb (Bioss, bs-1453R) (Bioss, bs-0061R-2). Hangzhou Fdbio Science provided anti-rabbit/mouse HRP (horseradish peroxidase)-conjugated secondary antibodies (FDR007, FDM007). The cells were lysed using a radio-immunoprecipitation assay to obtain the total protein (RIPA). Total protein was quantified using the Bradford assay and denatured by boiling at 105°C prior to Western blotting. Using an electro-blotting apparatus, equal amounts of protein were separated on SDS-PAGE gels and transferred to a polyvinylidene fluoride (PVDF) membrane (Bio-Rad, Hercules, CA, USA). The membrane was blocked for 60 minutes at room temperature with 5% bovine serum albumin (BSA) before being incubated with the primary antibody overnight at 4°C. The membrane was then incubated for 1 hour at room temperature with an HRP-conjugated secondary antibody (RT) [3].

An enhanced chemiluminescence substrate was used to detect the bound antibodies (Bio-rad, United States). The FluorChem E System was used to capture the images (Protein-sample, Santa Clara, CA, USA) and examined with ImageJ software (NIH, Bethesda, MD, USA). An RNA isolation kit was used to lyse the cells. qRT-PCR was used to detect the level of mRNA expression, as previously reported. The relative expression of the viral gene was determined using a classical 2-CT method with LightCycler 480 instrument software, with the cellular GAPDH gene serving as the internal control. For the RT and qRT-PCR experiments, the PrimeScriptTM RT Reagent Kit and the GoTaq® qPCR Master Mix (Promega, Madison, WI, USA) were used, respectively. The qRT-PCR primer sequences can be obtained upon request. The A549 cells were cultured for 24 hours on 35 mm confocal dishes until they reached 80% confluence. These cells were then pre-treated for 3 hours at 37°C with CPZ (20 M), MCD (20 M), and nisoldipine (20 M). CPZ is a clathrin-mediated endocytosis inhibitor [4].

MCD is a caveolin-mediated endocytosis inhibitor. Following that, the A549 cells were labelled with endocytic markers (25 g/mL Tf-568 or 2 g/mL CTB-FITC) and incubated at 4°C for 1 hour. The A549 cells were then incubated for 15 minutes at 37°C. Finally, the A549 cells were fixed for further examination. Images were captured with an Airyscan Zeiss LSM 800 Confocal Laser Scanning Microscope. All tests were carried out. in three different ways At least three independent experiments were carried out. The results are presented as mean standard deviation (SD). GraphPad 5.0 Prism software was used for all statistical analyses of the data. Two groups were analysed statistically, including the Student's t-test, and the other groups were analysed using one-way ANOVA with or without Tukey-Kramer multiple comparisons. A p value of 0.05 was considered statistically significant in all cases and was denoted with an asterisk. All results are based on three replicate experiments (ns, no significance) [5].

Conclusion

Finally, we demonstrated that nisoldipine, an existing drug used to treat hypertension, effectively inhibits IAV entry without causing significant cytotoxicity. Following that, a mechanism study revealed that nisoldipine effectively inhibited IAV entry via extracellular Ca^{2+} influx, involving both clathrin-mediated and clathrin-independent endocytosis. This research indicates that nisoldipine could be developed as a future therapeutic option for the treatment and prevention of IAV infection.

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