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Neuraminidase inhibitors reduce nitric oxide production in influenza virus-infected and gamma interferon-activated RAW 264.7 macrophages

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Abstract:
The influenza virus (influenza) infection causes an intense infiltration of pulmonary tissues by macrophages, which abundantly generate a free radical, nitric oxide (NO) resulting in lung damage. Neuraminidase inhibitors (NIs) restrict influenza virus replication but whether they can suppress NO production within macrophages is unknown. RAW 264.7 macrophages were exposed to interferon-gamma (IFN-γ), live influenza (A/PR/8/34) or a combination of both and were treated with NIs (oseltamivir or zanamivir). Results revealed that the drugs reduced a synergy between influenza and IFN-γ in NO synthesis within the cells at all of the used concentrations (0.01, 0.1, 1 μg/ml). In contrast to zanamivir, this effect occurred in a concentration-dependent manner with oseltamivir treatment. On the other hand, all concentrations of zanamivir significantly suppressed NO production in comparison to that upon the combined exposure only ($p < 0.05$). Both compounds also considerably decreased NO generation in the IFN-γ-stimulated macrophages, and zanamivir in the influenza-infected cells as well. However, neither of the drugs inhibited iNOS mRNA expression in the cells containing these stimulants. Additionally, the data indicate that a prodrug oseltamivir can be activated *in vitro* within the macrophage cultures. These findings are important for designing treatment approaches to limit pulmonary inflammation during influenza infection.

Key words:
influenza virus, interferon-gamma, macrophages, nitric oxide, neuraminidase inhibitors, oseltamivir, zanamivir