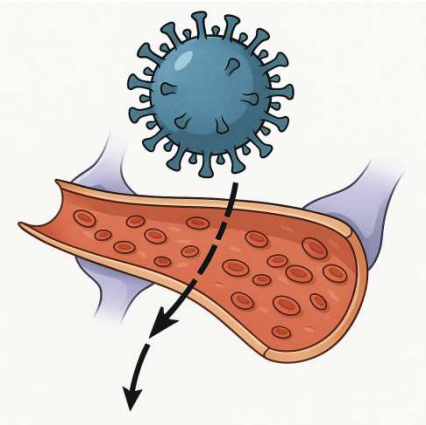
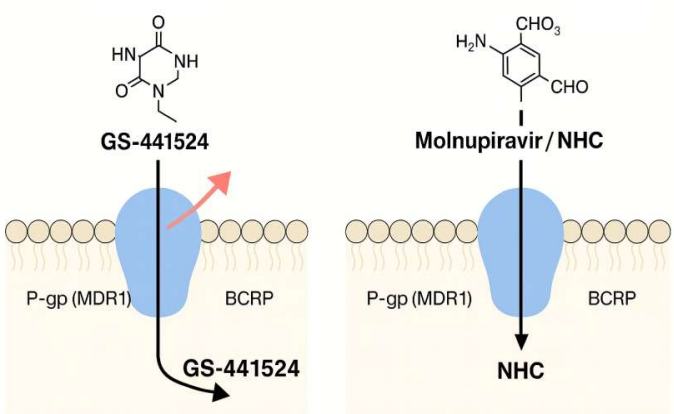
Antiviral Efficacy of Molnupiravir in the Neurological Form of FIP



Feline coronavirus (FCoV), particularly after mutating into the FIPV form, is capable of replicating within the central nervous system (CNS) (Pedersen, 2014a; Rissi, 2018). During this process, the virus infects cells of monocyte–macrophage origin and reaches the brain tissue via these cells (Dewerchin et al., 2005). Marked vasculitis, edema, and pyogranulomatous inflammation develop, especially in the meninges, brainstem, and around the optic nerve (Mesquita et al., 2016; Rissi, 2018; Tasker et al., 2023). As a result of these lesions, neuronal transmission is disrupted; clinically, ataxia, nystagmus, blindness, and behavioral changes are observed (Foley et al., 1998; Rissi, 2018). Although FCoV generally crosses the blood–brain barrier to a limited extent, in the FIPV form, inflammation-mediated increases in barrier permeability facilitate viral replication (Pedersen, 2014b; Dickinson, 2020).

In a microdialysis-based pharmacokinetic study conducted by Chang et al. (2023), it was reported that following intravenous administration of molnupiravir at a dose of 100 mg/kg to rats, both molnupiravir and its active metabolite β-D-N4-hydroxycytidine (NHC) were detected in brain tissue. The drug was shown to be rapidly converted to NHC in the systemic circulation, with NHC reaching brain tissue within 20–40 minutes, and the brain-to-blood distribution ratio (AUC_{brain}/AUC_{blood}) was determined to be approximately 0.8%.

The extent of molnupiravir penetration into brain tissue corresponds to approximately 0.8% of total systemic exposure. This ratio indicates that although only a small fraction of the administered dose reaches the brain tissue, this penetration is quantitatively meaningful and sufficient to exert antiviral activity. Indeed, the maximum concentration of NHC in brain tissue (C_{max} ≈ 0.7 µg/mL) was found to be above the reported effective concentration range for coronaviruses (IC_{50}: 0.08–0.3 µM), suggesting that the drug has therapeutic potential at the level of the central nervous system (Chang et al., 2023).



ATP-dependent efflux pumps located on the apical surface of blood–brain barrier (BBB) endothelial cells—primarily P-gp (MDR1, ABCB1) and BCRP (ABCG2)—transport many pharmaceutical compounds and drugs back into the vascular lumen via ATP hydrolysis after they enter the endothelial cell, thereby reducing their intrabarrier concentration (Begley, 2004; Abbott et al., 2010). These pumps, particularly, limit the passage of nucleoside analogues into brain tissue (Wang et al., 2022).

Molnupiravir and its active metabolite NHC are not substrates of efflux transporters; this property allows the drug to more effectively cross the central nervous system and other tissue barriers. Findings from the study by Chang et al. (2023) demonstrated that administration of P-gp (MDR1) and BCRP inhibitors did not significantly alter the brain-to-plasma ratio of NHC. This indicates that NHC is not a substrate of efflux transporters or is not expelled by these pumps to a meaningful extent. According to the European Medicines Agency (EMA) assessment report, molnupiravir is able to exhibit high intracellular bioavailability without being subject to efflux-dependent restriction (EMA, 2022).

In contrast, GS-441524 has been shown to be a substrate of efflux pumps (e.g., P-gp, BCRP) in regions such as the blood–brain barrier where these transporters are highly expressed (Wang et al., 2022). Overexpression of P-gp reduces intracellular nucleotide triphosphate levels of GS-441524 (Vangeel et al., 2021; Wang et al., 2022). This leads to reduced antiviral efficacy (Liu et al., 2018); however, this represents host cell resistance rather than viral resistance (Vangeel et al., 2021). A similar mechanism is known in chemotherapeutic agents as MDR1-mediated multidrug resistance (MDR) (Sharma et al., 2022). This phenomenon may limit the ability of GS-441524 to reach sufficient tissue concentrations at these barriers (Wang et al., 2022).

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