

治療阿茲海默症腦能量不足：

一種以 ENT1 抑制為核心的新療法

Policy Practices and Targeting Brain Energy Deficiency in Alzheimer's Disease:

A Novel Pharmacological Strategy via ENT1 Inhibition

Alzheimer's disease (AD) remains the leading cause of dementia in aging societies, yet current pharmacological interventions provide only modest benefits. There is an urgent unmet need for innovative therapies. One promising direction is restoring brain energy homeostasis. Adenosine, a central regulator of mitochondrial activity and cellular metabolism, is dysregulated in AD. The equilibrative nucleoside transporter 1 (ENT1), which controls adenosine flux, thus represents a novel drug target. Through natural product-guided discovery from *Gastrodia elata*, we identified T1-11, which led to the development of J4, an orally bioavailable ENT1 inhibitor. J4 was evaluated across four AD mouse models using cognitive tests, biochemical profiling ($A\beta$, tau, oxidative stress, neuroinflammation), metabolic assays, and sleep behavior analysis. Briefly, post-symptomatic J4 treatment markedly improved cognition and memory, reduced $A\beta$ and pathogenic tau accumulation, alleviated oxidative stress and neuroinflammation, restored mitochondrial and glucose metabolism, and corrected sleep disturbances. In summary, ENT1 inhibition offers a first-in-class pharmacological strategy that directly targets brain energy deficiency in AD. J4 is a stable, cost-effective compound suitable for scale-up, making it a promising candidate for clinical development and addressing a critical unmet therapeutic need.