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HIV and cocaine converge on RSK1 to induce GSK3 β -independent tauopathy during HAND

Background: Tau, a microtubule-associated protein, plays a critical role in maintaining neuronal function by stabilizing axonal microtubules and supporting efficient cargo transport necessary for synaptic activity and neuronal survival. When aberrantly phosphorylated, Tau loses its microtubule-binding capacity, adopts pathological conformations, and accumulates into insoluble neurofibrillary tangles. Emerging evidence indicates that HIV infection, even in well-controlled people with HIV (PWH), can disrupt the normal regulation of Tau phosphorylation, potentially contributing to neurotoxicity and HAND.

Rationale/Significance: HIV infection and drugs of abuse disrupt central nervous system (CNS) homeostasis, contributing to neurotoxicity and neurocognitive impairment. However, a comprehensive understanding of the underlying molecular mechanisms is essential for the rational development of targeted therapies.

Hypothesis: We hypothesized that HIV and drugs of abuse converge on RSK1 signaling to induce aberrant Tau phosphorylation through a previously unrecognized GSK3 β -independent pathway of Tauopathy that contributes to HAND and offers a novel therapeutic target for individuals with HIV (PWH) and /or those who use illicit drugs.

Results and discussion: In this study, we delineate the molecular pathway by which HIV and cocaine promote Tau phosphorylation at Ser396 (p-Tau S396), a key marker of Tau-associated neuropathology. We demonstrate that HIV robustly upregulates and activates ribosomal S6 kinase 1 (RSK1), which subsequently phosphorylates GSK3 β at Ser9 (p-GSK3 β S9), leading to its inactivation. Notably, Tau phosphorylation occurred despite GSK3 β inactivation, indicating a GSK3 β -independent mechanism. We further show that HIV-induced RSK1 acts upstream of AKT1, as AKT1 inhibition does not alter RSK1 activity. Similarly, cocaine activates RSK1 and strongly stimulates AKT1; however, Tau phosphorylation again coincides with GSK3 β inactivation, reinforcing the conclusion that this process is independent of GSK3 β activity. Collectively, our findings identify RSK1 as the principal mediator of HIV- and cocaine-induced Tau phosphorylation and uncover a previously unrecognized GSK3 β -independent pathway of Tauopathy driven primarily by RSK1.

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