Small Molecule Kinase Inhibitors Reduce Hyperphosphorylated Tau in Alzheimer Disease Mouse Models

Several neurodegenerative disorders, such as Alzheimer disease, involve the accumulation of hyperphosphorylated Tau as paired helical filaments in the central nervous system. Treatment options that target hyperphosphorylated Tau do not exist. In this Paper of the Week, a team led by Kenneth S. Kosik at the University of California at Santa Barbara explored the possibility that diaminothiazoles, a class of small molecules, can act as inhibitors of kinases that phosphorylate Tau. They studied the toxicity and immunoreactivity of several diaminothiazoles that targeted two key kinases, CDK5/p25 and GSK3β, in two mouse models. The investigators found that the compounds could efficiently inhibit the enzymes with hardly any toxic effects in the therapeutic dose range. The diaminothiazoles improved the memories of the mice during a fear-conditioning assay and reduced the amount of the paired helical filaments in their brains. The authors concluded, “Given the contribution of both CDK5/p25 and GSK3β to Tau phosphorylation, effective treatment of tauopathies may require dual kinase targeting.”

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Small Molecule Kinase Inhibitors Reduce Hyperphosphorylated Tau in Alzheimer Disease Mouse Models ♦: Diaminothiazoles Modify Tau Phosphorylation and Improve the Tauopathy in Mouse Models

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