Progressive supranuclear palsy (PSP) is a sporadic and progressive neurodegenerative disease, most often leading to a symmetric, akinetic-rigid syndrome with prominent postural instability, vertical supranuclear gaze palsy, and cognitive decline. It belongs to the family of tauopathies and involves both cortical and subcortical structures. There is evidence from laboratory as well as in vivo studies suggesting that mitochondrial energy metabolism is impaired in PSP. Furthermore, several findings suggest that a failure in mitochondrial energy production might act as an upstream event in the chain of pathological events leading to the aggregation of tau and neuronal cell death. Agents targeting mitochondrial dysfunction have already shown a positive effect in a phase II study; however, further studies to verify these results need to be conducted. This review will focus on the pathophysiological concept of mitochondrial dysfunction in PSP and its possible role as a therapeutic target.