Stress

Role of mitochondrial fission in stress susceptibility

Depression is currently one of the most widespread disorders affecting today's stressful society, but the mechanisms underlying this condition remain unknown. With the brain of an adult human spending around 20% of the total available energy, it is easily prone to energy deficiency, which can impair neuronal transmission. To comply with this energy demand and ensure transmission maintenance, synapses synthesize ATP locally, a process which is much more efficient when coming from mitochondrial oxidative phosphorylation instead of glycolysis alone. With such a delicate energetic balance needed, alterations in ATP levels and mitochondrial dysfunction have been linked to depression. A study in *Nature Metabolism* shows how chronic stress promotes mitochondrial fission in the medial prefrontal cortex (mPFC) of male mice, leading to mitochondrial dysfunction and depressive-like behavior.

Using behavioral, biochemical and imaging techniques, the team studied the role of dynamin-related protein 1 (Drp1), a protein known for its critical role in mitochondrial fission. After being exposed to an aggressive CD-1 mouse and living with a CD-1 individual for 10 days, C57BL/6J animals were categorized as susceptible or resilient to chronic stress, depending on their social interaction and disinterest in sucrose water. Control animals were only housed with conspecifics. Susceptible animals showed lower ATP levels and increased damaged mitochondria in the mPFC compared with control animals, resulting in more mitochondrial fission. Increased mitochondrial fission, leading to energetic deficits, was linked to deficits in synaptic communication in the mPFC in susceptible animals. In addition, in susceptible animals, the active phosphorylated form of Drp1 was increased in the mPFC. When Drp1 was knocked down, the mice showed less activation of mitochondrial stress signaling pathways and less depression-like symptoms. In contrast, Drp1 overexpression in the mPFC increased social avoidance and decreased interest in sucrose. Finally, pharmacological restoration of ATP synthesis had an antidepressant effect.

These results identify the role of Drp1-mediated neuronal mitochondrial fission in synaptic transmission and suggest that targeting mitochondrial fission is a potential promising strategy to alleviate depressive-like symptoms.

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