Unearthing a pathway to brain damage

February 25 2011

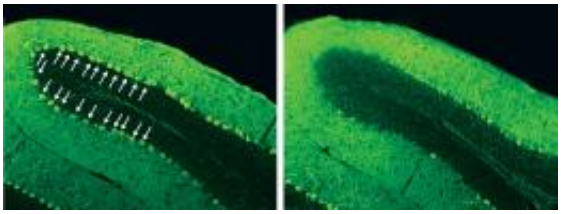

Figure 1: Cross-sections of the brain's cerebellum showing normal neurons (left) and ones lacking IP3R1 (right), which results in abnormal cell death and brain damage under ER stress conditions. Credit: 2011 Elsevier Inc.

Neuroscientists have long suspected that abnormal calcium signaling and accumulation of misfolded proteins cause an intracellular membrane-bound organelle called the endoplasmic reticulum (ER) to trigger the abnormal death of cells implicated in many neurodegenerative diseases. However, the underlying mechanisms have proved elusive.

The ER is crucial for synthesizing proteins and maintaining their quality, and also acts as a reservoir of calcium ions essential for numerous cellular events. However, it is sensitive to alterations of surrounding environments, causing a process called ER stress.

Katsuhiko Mikoshiba and Takayasu Higo at the RIKEN Brain Science Institute, Wako, and their colleagues now report that a calcium channel called IP3 receptor type1 (IP3R1), which mediates the release of calcium ions from ER, is destroyed by ER stress and that this induces

neuronal cell death and brain damage1 (Fig. 1).

Using a calcium imaging technique, the researchers revealed that IP_3R1 released less calcium in cultured neurons treated with an ER stress inducer than in controls. To investigate the significance of this dysfunction, they bred mice lacking the gene for IP_3R1, which caused brain damage under ER stress conditions.

In an exploration into how ER stress impairs IP_3R1 and induces neuronal cell death. Mikoshiba and colleagues identified GRP78, a molecular 'chaperone' that normally regulates the cellular response to misfolded proteins, as an interacting partner of IP3R1. RNA interference experiments revealed that GRP78 positively regulates the assembly of IP_3R1, which consists of four subunits. They also found that this interaction was inhibited under ER stress conditions.

In a further set of experiments, the researchers then examined the involvement of the interaction in neurodegenerative diseases using a mouse model of Huntington's disease (HD). They found that both the protein interaction and IP_3R1 channel activity were significantly impaired in parts of the brain most affected in HD.

The findings demonstrate a novel mechanism by which ER stress impairs the regulation of IP_3R1 by GRP78. Mikoshiba and Higo propose that IP3R1 functions to protect the brain against stress and that the link between ER stress, IP_3/calcium signaling, and neuronal cell death is associated with neurodegenerative disease.

"It has been suggested that neurodegenerative conditions including Huntington's disease are associated with deranged calcium signaling and ER stress," says Mikoshiba. "We hypothesize that IP_3R1 functions to protect the brain from ER stress, so development of a method to restore or enhance IP_3R1 could prevent disease progression or alleviate the

symptoms. Our findings might be applied to other neurodegenerative diseases such as Alzheimer's disease."

More information: Higo, T., et al. Mechanism of ER stress-induced brain damage by IP3 receptor. *Neuron* 68, 865–878 (2010). www.cell.com/neuron/abstract/S0896-6273(10)00917-7

Provided by RIKEN