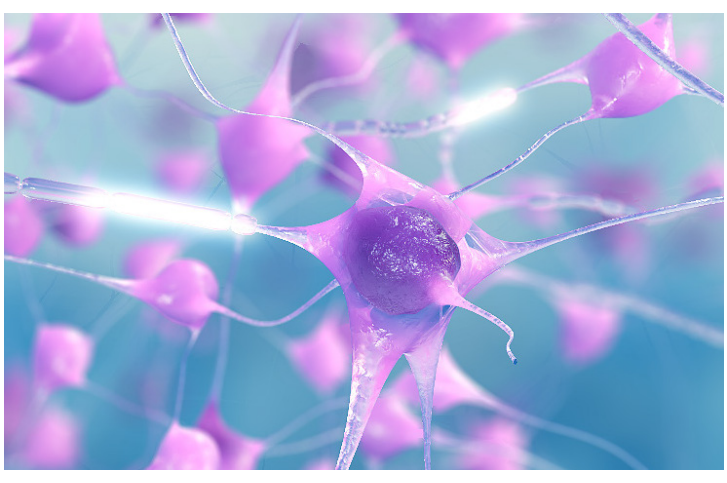
Bristol Myers Squibb®

The integrated stress response and the role of eIF2B

The integrated stress response (ISR) is a mechanism within cells to help them adapt to problems in their environment, such as insufficient nutrients and production of misfolded proteins, to restore balance and stay healthy.

When activated by different stress stimuli, the ISR:



Healthy neurons

↓ Temporarily **turns DOWN** the production of most proteins

↑ **Turns UP** the production of select proteins and drives a pattern of gene expression important to cell recovery and survival

This mechanism, when activated for **short periods of time**, is helpful to cells but can become harmful during chronic activation. When it cannot restore balance, the ISR can initiate cell death and play a role in the worsening of neurodegenerative diseases.[1-3]

The role of eIF2B

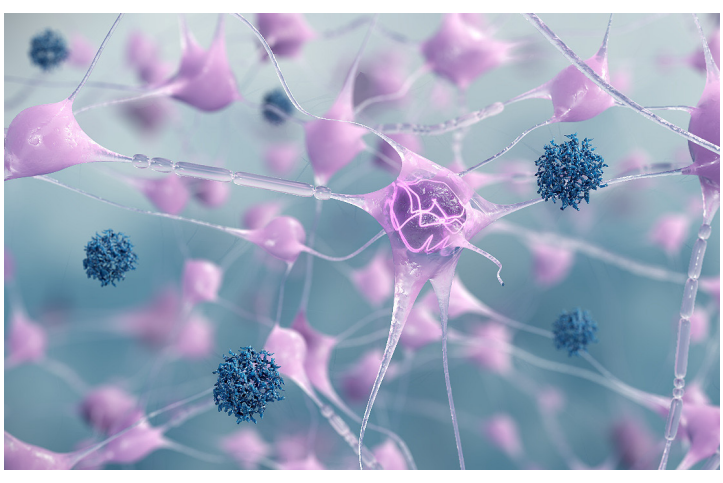
Eukaryotic translation initiation factor 2B (eIF2B) is an important regulator in the process of making proteins in cells, known as protein translation. Typically, in its active form, eIF2B facilitates the continued production of proteins needed by healthy cells to maintain their function.

When the ISR is **activated**, it reduces general protein production by **inhibiting eIF2B**.[1,2]

eIF2B

The ISR in neurodegenerative diseases

Many neurodegenerative conditions are associated with significant cell stress due to misfolded proteins in neurons (a type of cell in the brain). In Alzheimer's disease, for example, misfolded proteins including beta-amyloid and tau trigger the ISR.[1,3]



Cell dysfunction and death

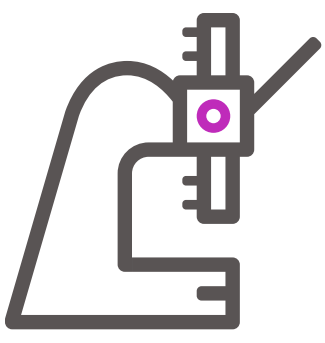
The continued and overwhelming presence of misfolded proteins in cells results in[1-3]:

- Long-term activation of the ISR
- A lasting decline in proteins needed for proper cell function
- Cell dysfunction and even death

Normal protein production is also required for the formation of new, long-term memories within the brain region called the hippocampus. Consequently, **chronic activation of the ISR can inhibit the formation of long-term memories**.[1]

Research implications

Recent research into the causal human biology of neurodegenerative conditions has suggested that **turning down the ISR** may help slow neurodegeneration and improve cognitive function.[1]



Researchers are **targeting eIF2B** as a potential way to help overcome long-term activation of the ISR and its harmful effects.

Preclinical research has shown that **activating eIF2B** may preserve neuronal structure and synaptic function by restoring normal protein homeostasis. This could result in improved long-term memory and address other neurological symptoms such as cognitive decline across a range of diseases, including Alzheimer's disease.[4-7]

Bristol Myers Squibb is committed to rapidly advancing an innovative and diverse pipeline in neuroscience. With a deep focus on causal human biology, we are researching key pathways to slow or stop disease progression and treat symptoms to achieve the greatest impact for patients.

REFERENCES

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