Decoding ISRIB - Pioneering Advances in Neurological Health and Nootropics

History & Mechanism of Action

ISRIB was discovered in by researchers at the University of California, San Francisco in 2013 in the Lab of Peter Walter.[1] In the first publication about ISRIB, it was reported to increase cognitive function in mice, which hence led the pathway to further studies focusing on the nervous system. In 2015, the rights were licensed to Calico Life Sciences LLC where testing on mice was intensified and the field of research was broadened to other cell types and the exact mechanism of ISRIB's action.

On a molecular level, the authors of the first studies concluded that ISRIB inhibits the phosphorylation of eIF2 (eukaryotic initiation factor 2), a protein with critical important for starting protein biosynthesis in humans. When a cell is under stress, it usually turns protein biosynthesis off by phosphorylation of eIF2. ISRIB can diminish this ability by inhibiting the phosphorylation of eIF2. Thus, the cell continues to produce proteins even under stress. A later perspective in the mechanisms of action found that ISRIB does not directly inhibit the phosphorylation of eIF2, but rather binds to the beta subunit of eIF2, which promotes the activation of the alpha-subunit, which increases the activity of eIF2 overall.[2] More mechanistic studies at a later time have further elucidated the exact mechanism by which ISRIB influences the stress response. [3]

In 2019, a study found that ISRIB is only effective in suppressing the stress response when stress is low. In higher stress scenarios, ISRIB is overpowered by the stress signal inside the cell and protein synthesis is halted despite the presence of ISRIB.[4]

Use of ISRIB in Studies on the Nervous System and Neurological Disorders

In the original publication in which ISRIB was discovered, the authors reported that it was a potent inhibitor of the PERK (protein kinase R (PKR)-like endoplasmic reticulum kinase) signaling pathway, which is a mechanism by which a cell can sense stress in form of unfolded proteins in the endoplasmic reticulum. As result, stressed cells treated with ISRIB show a decreased adaptation to the stress and as results a lower survivability. These results were achieved on isolated cells though.

However, the authors performed studies with mice treated with SIRIB in this initial study, since it was known previously that phosphorylation of eIF2 in a subset of neurons impairs memory function in mice. And indeed, the mice injected with

ISRIB had a better long-term memory function compared to the control animals in different learning scenarios, which was consistent with the previous reports and assumptions. The authors explanation of why ISRIB does enhance cognitive function is because neurons need to synthesize new proteins for learning and since ISRIB does lead to the preservation of protein synthesis under condition where it would usually be switch off, it therefore increases learning ability. Additionally, it was found that ISRIB has a plasma half-life of 8 hours and can cross the blood brain barrier.

Soon after its discovery, ISRIB was shown to prevent the death of neurons in mice that suffered from a prion disease. Prions are misfolded proteins, that accumulate in cells and can cause damage if the concentration of misfolded proteins gets too high. It was found that ISRIB could only partially restore the cell function back to normal, while another previously tested molecule "GSK2606414" did fully restore the cell function back to normal.[5] This molecule has a different mechanism of action, it directly prevents the phosphorylation of eIF2. The damage caused by protein aggregates in the brains constitutes problem in many neurological disorders, including Alzheimer's disease. As one might expect from these results, ISRIB did also increase enhances cognition in an Alzheimer disease model in rats, shown by later studies.[6] It was also shown ISRIB can even reverse some sign of stress in isolated cells after they have already been formed.[7]

Research on the topic of other types of neurodegenerative diseases showed that ISRIB can potentially be used to treat vanishing white matter disease, a syndrome based on mutations of eIF2b. ISRIB can reduce the effect of these mutations, leading to a normal cell function in some cell lines. While this has not been tested on living organisms with vanishing white matter disease, the experiments on cells in this study indicate a potential benefit.[8]

In 2020, another study on mice, authored by the original discoverer Peter Walter, found reverses in memory deficits and ameliorates working memory in old mice. At the cellular level in the hippocampus, ISR inhibition rescues intrinsic neuronal electrophysiological properties. The density of neurons in the spine and the reduction of immune activity was also was observed. The authors did conclude that ISRIB may be a compound suitable for human use, especially in the elderly in order to retain cognitive function for a longer period of time.[9]

A study of mice suffering from amyotrophic lateral sclerosis (ALS) has shown to improve the survival of neurons, which are critical for movement and coordination. There is good evidence that ALS is triggered by the accumulation of proteins in the endoplasmic reticulum, which leads to the activation of the integrated stress response and eventually, cell death. As previously described, ISRIB seem to prevent neural death by diminishing the integrated stress response.[10] A further disease resulting in the death of neurons is the MEHMO-Syndrome. It is a congenital disorder leading to intellectual disability, seizures and obesity. A cell model of the disease showed increased neuronal survival in the presence of ISRIB, which may lead to better clinical outcome in humans suffering from MEHMO-Syndrome.[11]

Lastly, ISRIB may also be used to combat the symptoms of depression. It was found that ISRIB reduces the level of pro-inflammatory processes in the brain, which are generally associates with a depression.[12]

ISRIB Increases Neuron Survival After Traumatic Events

In 2017, researchers treated mice which had suffered simulated

traumatic brain injury with ISRIB and found these mice were as good in long term memory tasks as healthy controls, even if ISRIB was administered two weeks after the injury. This may indicate a human use for patients with traumatic brain injuries.[13] Similar results were achieved if mice experienced traumatic spinal cord injury.[14]

Another important source of neurological deficit in humans are strokes, caused by arterial blockage in the brain. A study conducted in 2023 found that ISRIB (along with another tested drug called stiripentol) did significantly improve the motor function and memory deficit in rats that recently experienced a stroke.[15]

Other Medical Fields

While most studies with ISRIB focus on neuronal survival, the protein eIF2 is present in every cell, so there is good reason to believe that ISRIB could be applied in different fields as well. A group focused on pulmonary fibrosis, a serious disease with worsening lung function. It was showed that ISRIB does facilitate the repair of damaged lung tissue into functional respiratory tissue instead of conversion into fibrotic tissue, as would be an expected transition in pulmonary fibrosis.[16] This indicates ISRIB could be an effective treatment for pulmonary fibrosis, a condition that is hard to treat even with modern methods.[17]

Another study explored ISRIBs effect in a completely different direction. The authors showed that old mice can more effectively burn calories during cold exposure to stay warm utilizing their brown fat tissue after an administration[18] of ISRIB. Their explanation is that usually the brown fat cells would shut themselves of under these conditions because of the high stress they experience. ISRIB however deactivates this stress response and leads to a normalized cell function and more heat generation.

Cancer

Interestingly, another group of researchers combined ISRIB with the proteasome inhibitor bortezomib to test the effect on cancer cells. Bortezomib activates the integrated stress response and the addition of ISRIB increases cell survival, as expected. However, in breast cancer cells this combination leads to a special cell death mode called paraptosis. At this point, it is not clear why this happened, but it may point towards a new anti-cancer treatment.[19] Furthermore, Imatinib, a tyrosine-kinase inhibitor developed to treat chronic myelogenous leukemia, a type of blood cancer, was combined into one treatment with ISRIB in mice. They showed the addition of ISRIB did aid in the elimination of cancer cells and they hypothesized that Imatinib will benefit from the additional administration of ISRIB in human cancer patients.[20]

Cisplatin, a common tumor treating agent, shows a lower cell toxicity, if combined with ISRIB. Similar to the previous study, this effect is more pronounce in healthy cells compared to tumor cells, making the addition of SIRIB to common chemotherapy treatment regimes a potential strategy to increase the tumor selectivity of chemotherapeutics.[21]

Conclusion

ISRIB does show many positive effects overall and there is a lot of experimental evidence in mice that show the efficacy of ISRIB in a variety of conditions. ISRIB has mostly been tested in studies focusing on neurological function and its effects are well established in this field. However, newer studies suggest it can also be effective on tissues of a completely different origin and for different indications. However overall, it seems that ISRIB will only be a suitable substance to consume if some tissues suffer from a stress which will result in an impaired cell function, but only to a certain degree. If the stress is too great, the effect of ISRIB seems to vanish.

Impaired cell function usually is a problem in older individuals due to the lower effectivity of their general cell population. Hence, ISRIB might be a good substance to consume for older individuals as base medication to counter a variety of disadvantages that aging brings with itself like lower muscle strength, reduced metabolic rate, thinning of skin or even the greying of hair.

However, there are no clinical trials conducted to this day, which may be due to the fact that the economic risk for market introduction is seen as too high, as

use would likely be mostly confined to recreational use in older individuals. A few studies show that it might be a useful substance for traumatic events like a stroke and rare neurological disorders, which indicates it might be useful for clinical practice later.

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