Upending textbook science on Alzheimer's disease

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Alzheimer's disease is caused by the build-up of a brain peptide called amyloid-beta. That's why eliminating the protein has been the focus of almost all drug research pursuing a cure for the devastating neurodegenerative condition.

But that may be counterproductive, says Dr. Inna Slutsky of Tel Aviv University's Department of Physiology and Pharmacology, Sackler Faculty of Medicine. Her recent research demonstrates that amyloid-beta is also necessary to maintain proper brain functioning.

These findings may shake the foundations of Alzheimer's research.

In a new study published this month in *Nature Neuroscience*, Dr. Slutsky finds that amyloid-beta is essential for normal day-to-day information transfer through nerve cell networks in the brain. "If this protein is removed from the brain," says Dr. Slutsky, "as some drugs in development attempt to do, it may cause an impairment of neuronal function, as well as a further and faster accumulation of amyloid-betain Alzheimer's."

A reset button for drug researchers

Without amyloid-beta, a normal product of cellular metabolism, one's ability to learn and remember could be profoundly damaged, so drugs currently in development to eliminate amyloid-beta could be rendered

obsolete. With Dr. Slutsky's research, a leap in understanding the cause and development of Alzheimer's disease, however, new, more effective drug therapies could be developed.

By studying synapses in brain slices of healthy mice and in neuronal networks growing in vitro, Dr. Slutsky and her team determined that there is an optimal amount of amyloid-beta needed to keep the neurons working well. Her students Efrat Abramov and Iftach Dolev found that if this precise balance is even slightly disturbed, the effectiveness of information transfer between neurons is greatly impaired.

"Synapses where neurons meet work as filters of information," says Dr. Slutsky. "What is really exciting for us is the fact that amyloid-beta peptide, believed to be toxic, regulates the type of information that neurons transfer."

A new way to prevent Alzheimer's?

The study of Dr. Slutsky's team suggests that the amyloid-beta protein belongs to endogenous molecules regulating normal synaptic transmission in the hippocampus, a brain region involved in learning and memory function. "There is a long list of neuromodulators that help synapses optimize information transfer," she says. "Intriguingly, amyloid-beta seems to be able to modulate this filter and shape its properties."

The new study is discouraging news for those Alzheimer drugs that attempt to block or remove the amyloid-beta aggregation process currently in clinical trials, Dr. Slutsky believes. "Our data shows that after the release of amyloid-beta, synaptic activity in the neurons is increased through a positive feedback loop. Disrupting this positive feedback loop, I believe, is the key for prevention of the earliest signs of Alzheimer's."

Source: Tel Aviv University (news : web)