Zebrafish reveals central regulator for development of brain histamine system

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Research has shown that mutations in the psen1 gene are common in the familial forms of Alzheimer's disease, and the Presenilin-1 protein that the gene encodes is known to be involved in the cleavage of the amyloid precursor protein. In Alzheimer's disease the amyloid precursor protein is not cleaved the normal way, and the protein accumulates in the brain damaging neuronal tracts and neurons. It is still unknown if the psen1 gene is involved in the etiology of Alzheimer's disease via another mechanism.

Professor Pertti Panula's research team at the University of Helsinki has elucidated the role of psen1 gene in the development of the neuronal histamine system and its modulation. Histamine is one of the neurotransmitters, which all are essential for cognitive functions, which in turn are impaired in Alzheimer's disease. The histamine system is altered during the progression of Alzheimer's disease.

In the study the zebrafish was used as a model organism. The rapidly developing zebrafish is suitable as a model organism, as its transparency allows researchers to study the development and function of vital organs. To study the function of psen1 gene, zebrafish that did not produce functional Presenilin-1 protein were generated. Despite the fact that the fish lacked functional Presenilin-1 they were viable and developed until adulthood.

The lack of Presenilin-1 protein induced a change in the behavior of the larval zebrafish, they did not as normal fish react to fast changes in the

light intensity. "Based on previous research we know that this change in behavior is associated with lack of histamine in the brain", Panula explains.

In adulthood the motor behavior of the mutant zebrafish differed from the normal fish: the fish swam by the edges of the arena that was available and avoided the inner part. Previous studies from the group have shown that this behavioral alteration also is due to changes in the histamine system.

The researchers found that larval fish lacking Presenilin-1 protein had significantly fewer histamine neurons; in adulthood the histamine neuron number was significantly increased in these fish when compared with normal fish.

"These results reveal that the psen1 gene is a central regulator of the development of the histamine neurons and that the mutation can cause a persistent lifelong change in the neuronal histamine system. This is a very interesting finding", Panula states.

One interesting remaining question is from where the new histamine neurons arise in the brains of adult zebrafish. Are they newly differentiated stem cells or do other cells become histamine neurons? The answer is not known, but based on these results it is advisable to elucidate the role of Presenilin-1 protein in differentiation of stem cells also in the brains of mammals. "Mammals have stem cells in the hypothalamus, in the same area where the histamine neurons are located in all studied vertebrates", Panula comments.

Panula empathizes that the published study does not tell about an Alzheimer's disease mechanism in humans. The new knowledge on the function of psen1 gene and the development of the brain histamine system provided by the study is one step forward to understanding the

etiology of the disease.

"We perform basic research on molecular level, from where it is a long way to treatment of human diseases. This type of research provides the findings on which the treatments are finally based", Panula says.

Journal of Neuroscience has published the study.

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