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Researchers explore mechanism to stop ageing

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Elderly people of the town in a social event by Enramada

As medicine has improved, we are increasing our ability to treat disease and improve longevity. The deterioration of the body with age, though, is a whole other matter.

Scientists suggest that all we might need is some “house-keeping” of the brain, according to research just published in an early edition of the journal *PNAS* by a Portuguese team from the Centre for Neuroscience and Cell Biology (CNC) of the University of Coimbra.

The researchers might have also solved a 70-year old mystery: How can calorie restriction (a diet with low calories without malnutrition) delay ageing and increase longevity in animals from dogs to mice?

In their new study, Claudia Cavadas and her group have discovered that the key to this diet appears to be its ability to increase autophagy – the mechanism that recycles unwanted molecules in the cells, thereby avoiding malfunction in the hypothalamus, which has just been identified as the “control centre” for ageing. They also have identified the molecule that controls the process. It’s called neuropeptide Y (NPY), and its discovery raises the possibility that NPY could be used to develop techniques to control aging instead of just treating its consequences, like we do now.

The discovery may be a key to stopping the development of age-related neurodegenerative diseases such as Alzheimer’s and Parkinson’s, a huge step forward, considering that science has thus far been incapable of treating, stopping or even fully understanding them. And in a rapidly aging world, a better control of these kinds of problems can prove crucial for everyone’s survival.

In fact, according to the UN, in less than a decade, 1 billion people will be older than 60. In Japan, more than 30% of the population is older than 60 years old, and in Europe, 16% of the population is over 65. So it is clear that our increasingly aging population needs to be kept as healthy and active as possible, or it will be financially and socially impossible for the world to cope. It is no surprise, then, that research to understand and control the deteriorating effects of aging is now a priority.

One thing that has been clear for a while now is that autophagy (or better, a reduction of it) is at the centre of the aging process. Low levels of autophagy—that is, impaired cellular “house-keeping”—is linked to ageing and age-related neurodegenerative disorders, such as Alzheimer’s, Parkinson’s and Huntington’s diseases. This is easily explained as autophagy clears the cellular “debris” keeping neurons in good working order. The importance of the process in the brain is no surprise, since neurons have a lower ability to replenish themselves once they die or malfunction.

But about a year ago, there was a remarkable discovery that changed the field: The hypothalamus, which is a brain area that regulates energy and metabolism, was identified as the control centre for whole-body aging.

To Cavadas and her group, who have worked on aging and neuroscience for a long time, this was particularly exciting. They knew calorie restriction delayed aging and increased longevity and increased autophagy in the hypothalamus; but they also knew that it did the same to NPY and that mice without NPY did not respond to calorie restriction. Furthermore NPY, like autophagy, diminishes with age. All this, together with the discovery of the new role of the hypothalamus, suggested that this brain area and NPY were the key to the rejuvenating effects of calorie restriction.

So now all that was left was to connect the dots, and for that, the researchers started by taking

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neurons from the hypothalami of mice and growing them in a medium that mimicked a low caloric diet. They then measured rates of autophagy. As expected, autophagy levels in this calorie-restriction-like medium were much higher than normal, unless NPY was blocked, in which case the medium had no consequences on the neurons. So calorie restriction effect on the hypothalamic autophagy appeared to depend on NPY. To confirm this, the researchers then tested mice genetically modified to produce higher than normal quantities of NYP in their hypothalami. As expected, this led to higher levels of autophagy.

So calorie restriction seems to work by increasing the levels of NPY in the hypothalamus, which in turn triggers an increase in autophagy in its neurons, "rejuvenating" them and delaying aging symptoms. Cavadas and colleagues also identified the biochemical pathways involved in the NPY effect. This, however, is not the whole story, as it still does not explain why in some species, such as wild mice, calorie restriction has no effect.

But by adding a new piece to the puzzle of aging, the group's research is an important step toward delaying the the body's deterioration, allowing individuals to have healthier lives until the end, particularly with regard to the brain. Age-related neurodegenerative diseases seem to be unstoppable at the moment, and are not only an economic but also a huge social burden as patients became totally dependent on their families or the state.

In fact, in the US, more than 5 million people already suffer from Alzheimer's (1 million have Parkinson's), while in the UK this number is reaching 1 million. Just in the care of dementia patients, the UK health system is spending more than £26 billion yearly (the equivalent to 38 billion dollars or 36 billion Euros). Age-related neurodegenerative diseases are already the fourth highest disease burden in the western world, and growing.

It will be interesting to further understand the long-debated mystery of the mechanism behind calorie restriction, and test to see if it works on humans as some believe (it does not work, for example, on wild mice). In fact, during World War II in Europe, when food was short, there was a sharp decrease in heart diseases (which are age-related) that rapidly rose once the war ended. The same reduction is observed in Okinawa island in Japan, where people eat on average less 30% of calories than the rest of the country. Whether a coincidence or not, it should be interesting to know what that that means in our "junk-food" society.

Explore further:

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More information: "Neuropeptide Y stimulates autophagy in hypothalamic neurons." DOI: 10.1073/pnas.1416609112

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