As medicine has improved, increasing our ability to treat disease, so our longevity. The deterioration of the body with age, though, is a whole other matter. But apparently, all that might be needed is some "house-keeping" of the brain, according to research just published on 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 calorie restriction (a diet with low calories without malnutrition) can 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, avoiding their "clogging and malfunction - in the hypothalamus (which has just been identified as the "control centre" for ageing). They also have found the molecule that controls the process - called Neuropeptide Y (NPY) - raising the possibility that NPY could be used to develop ways to control ageing (instead of just treat its consequences like we now do).

The discovery can prove especially important to stop the emergence of age-related neurodegenerative diseases - such as Alzheimer's and Parkinson's - a huge step forwards considering that so far science has been incapable of treating, stopping or even fully understanding them. And in a rapidly ageing world a better control of this kind 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, already 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 ageing 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 ageing is now a priority.

An 85-year old Ivatan woman sitting at her house's door PHOTO by Anne Jimenez

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 ageing process - low levels of autophagy (so cells with impaired "house-keeping") are 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 cells "debris" keeping them in good working order. That the process is so important in the brain is no surprise either, because neurons are the cells less able to replenish themselves once one dies/malfunctions.

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

To Cavadas and her group, which have worked on ageing and neurosciences for a long time, the news was particularly exciting. Not only they knew that the only proved method to delay ageing and increase longevity - calorie restriction - increased autophagy in the hypothalamus but also that it did the same to the molecule NPY and that mice without NPY did not respond to calorie...
restriction. Furthermore NPY, like autophagy, diminishes with age.
All this, together with the new identified role of the hypothalamus suggested that this brain area and NPY were the key to the rejuvenating effects of calorie restriction.

So all that was left was to join the dots, and for that the researchers started by taking neurons from the hypothalamus of mice and put them growing in a medium that mimicked a low caloric diet, to then measure their autophagy. Like expected, their autophagy levels in this calorie restriction-like medium were much higher than normal. But if NPY was blocked, the medium had no consequences on the neurons. So calorie restriction's effect on the hypothalamic autophagy appeared to depend on NPY. To test this, next the researchers tested mice genetically modified to produce higher than normal quantities of NYP in their hypothalamus, and found higher levels of autophagy supporting their theory that autophagy was controlled by NPY.

In conclusion, calorie restriction seems to work by increasing the levels of NPY in the hypothalamus, which in turn trigger an increase in autophagy in these neurons, "rejuvenating" them and delaying ageing signs (by restoring their ability to control the whole-body ageing). Cavadas and colleagues also identified the biochemical pathways involved in NPY effect.

Although a major discovery this, however, will not be the whole story, as it still does not explain why in some species, like wild mice, calorie restriction has no effect

Nevertheless, by adding a new piece to the puzzle that is ageing, Cavadas and her group’s research is an important step to one day help delay the body deterioration signs, allowing individuals to have healthier lives until the end, and crucially, to keep a healthy brain. In fact, at the moment age-related neurodegenerative diseases seem to be unstoppable creating not only an economical but also a huge social pressure, as patients become totally dependent on their family or the state.

The scale of this is easily given by numbers with the US already having more than 5 million people suffering from Alzheimer’s (1 million with Parkinson’s), while in the UK this number is reaching 1 million. Just in the care of dementia patients, the UK health system is now spending every year more than £26 billion English pounds (the equivalent to 38 billion dollars or 36 billion euros).

Age-related neurodegenerative diseases are already the 4th highest disease burden in the western world and growing so it is easy to understand the importance of Cavadas and her group’ results.

It will be interesting also to further explore calorie restriction’s mechanisms, especially if we can show that it works in humans as some believe (we know that it does not work in all animals, like for example wild mice).

On humans during World War II in Europe, when food was short, it was reported a sharp decrease of heart diseases (which are age-related) that rapidly disappeared once the war ended. The same reduction is observed in Okinawa island in Japan, where people eat on average less than 30% of calories than the rest of the country.

Either a coincidence or not, it should be interesting to know once and for all if calorie restriction can in fact work on humans and now that we start to understand its mechanics we might be able to answer that. Also interesting will be to see, if effective on humans, what that would mean for our culture of “junk-food”.