PRESS RELEASE

A new study shows that rabbits are not resistant to infection by prions

➢ A project led by CIC bioGUNE shows that rabbits are susceptible to spongiform encephalopathies, neurodegenerative diseases caused by prions.

➢ The research, published in the journal PLOS Pathogens, used real prions regularly found in livestock species.

➢ The conclusions from this study are useful for correctly assessing the risks faced by some species intended for human consumption.

(Bilbao, 7 August 2015).- Research coordinated by the Center for Cooperative Research in Biosciences CIC bioGUNE has shown in vivo that rabbits are not resistant to spongiform encephalopathies, neurodegenerative diseases caused by prions.

The study, directed by the scientist Joaquín Castilla, continued for four years and was recently published in the prestigious journal PLOS Pathogens.

Prions are an abnormal and infectious version of the protease resistant protein PrP, which is found in its benign state in the neurons of all mammals. Whenever a prion - a word derived from an infectious protein particle - is introduced into a healthy organism, it acts on the normal form of the protein, causes its poor folding and converts it into a new prion. Accumulation of these abnormal and infectious proteins activates the neuronal death and triggers the aforementioned spongiform encephalopathies, neurodegenerative diseases which have no cure or treatment and receive this name due to the pierced aspect shown in the brain of sick animals. One of the most well-known is the bovine variant, popularly known as mad cow disease.

In order to carry out the research, the team at CIC bioGUNE, assisted by researchers from the Centre de Recerca en Sanitat Animal (CReSA) of the Autonomous University of Barcelona, designed a series of transgenic mice which had the gene that encodes the PrP protein replaced with the one corresponding to the rabbit.
“These models are smaller than leporidae ones, but represent the real rabbit very well and, due to their lower cost, enable us to carry out research with a higher number of specimens”, states Castilla.

The transgenic mice were then inoculated with real circulating prions from sheep, cow, mouse and deer and the researchers observed that the animals developed bovine spongiform encephalopathy and also scrapie, prion disease of sheep and goats. However, no infection occurred with the prion of the deer.

“For 40 years we thought that the protein of the rabbit could not be folded badly. However this is not the case and the latter is the first fact we have demonstrated. There is nothing in the protein of rabbit which makes it resistant to poor folding”, explains Castilla.

Led by Castilla in 2012, the team laid the first stone in confirming the infection of rabbits using a synthetic prion designed in the laboratory, but the current study involves the verification in vivo, with real prions found in livestock species.

“These conclusions must be taken into account in the feeding of the rabbits, especially if feeds containing animal protein are used”, reasons Castilla.

**Different studies, identical conclusions**

In addition to the research of the CIC bioGUNE, scientists from France's National Institute for Agronomic Research (INRA) have carried out a direct study with transgenic rabbits which had the gene of the PrP protein of ovine origin introduced. Subsequently, the researchers inoculated them with ovine prions and observed that six to eight months later the rabbits became ill with spongiform encephalopathy, therefore this study also concludes that there is no single element in rabbits which makes them resistant.

**Why is it so difficult to drive the rabbit insane?**

For four decades it was believed that leporidae were resistant to infection by prions based on the absence of spongiform encephalopathies in rabbits.

The most recent research has refuted that theory and until now has not been capable of revealing the reasons why the transmission of prion diseases in rabbits seems more difficult than for other mammals.

In the opinion of Joaquín Castilla, the absence of cases of rabbits with this illness could lie in the fact that the leporidae were not fed with foodstuffs derived from infected animal protein as occurred with other species.

Another of the keys lies in the age of the animal. Spongiform encephalopathies have a generally prolonged incubation period and the rabbits are sacrificed at very young ages.

"10 month-old cows never suffer from mad cow disease. The cases detected always occur in bovine specimens of advanced ages", reasons the expert.
Reaching a thorough understanding of prions

Joaquín Castilla's team has considerable experience in the field of prion diseases and, in addition to heading various studies, collaborates in international research.

It recently took part in research led by the Mario Negri Pharmacological Research Institute in Milan centred on fatal familial insomnia (FFI), a human prion disease of genetic origin which is only found in a few families around the world.

In this case, the illness does not occur due to the intake of products contaminated with prions, but that the gene encoding the protein has a mutation which makes it prone to poor folding.

Patients suffering from FFI cannot sleep, lose their internal balance and in the final stages fall into an irreversible coma and eventually die.

The study was focused on the understanding of the genetics of the illness and its spreading mechanism.

To date, experts knew that the same mutation of the gene could trigger two strains of different prions: one causing the genetic variety of Creutzfeldt-Jacob and the other responsible for FFI. To suffer from one illness or another depends on the polymorphism that accompanies the mutation.

In the current study, researchers have designed transgenic mice which have the mutant protein accompanied by each one of the polymorphisms and they have been able to prove that the animals developed two different diseases.

“Until now we did not have any model which would reliably reproduce this phenomenon, that is, how the same mutation results in two different diseases”, states Castilla.

The representation of the model is the first milestone of the study, however the researchers observed a second phenomenon: the prions generated for the experiment were capable of triggering the illness but were not infectious, one characteristic inherent in circulating prions which affect humans.

“This finding is significant because it shows that the mechanism by which prions propagate, or in other words infect, is different from the mechanism by which the prions cause the illness”, adds Castilla.

The expert believes that the finding is relevant to the understanding of the disease and the future development of therapies.

“It is no use blocking a prion to prevent it from propagating in the brain if it continues to be toxic. This model has shown that the mechanism by which the prion kills neurones is not related to the way in which it propagates”, argues Castilla.
About CIC bioGUNE

The Center for Cooperative Research in Biosciences CIC bioGUNE, with headquarters in the Bizkaia Science and Technology Park, is a biomedical research organization that conducts innovative research into the interface between structural, molecular and cell biology, focusing specifically on the study of the molecular bases of disease, to be used in the development of new diagnostic methods and advanced therapies.

Study references

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