the Fair Journal

The Hormone Chromogranin A Balances Gut Wall Function

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Original title
Chromogranin A regulates gut permeability via the antagonistic actions of its proteolytic peptides.[1]

Introduction
In diseases related to chronic inflammation such as; inflammatory bowel disease (IBD), irritable bowel syndrome, and celiac disease, patients suffer from a 'leaky' gut wall. Normally, the gut wall consists of a one-layer cell-wall with a mucus layer on top that protects you against invaders in the gut, such as pathogenic bacteria. If this protection is damaged, the bacteria are no longer kept outside and can now enter our body. This triggers an inflammatory reaction where white blood cells move towards the gut to kill the invaders and repair the damaged or 'leaky' gut wall. In the case of chronic gut inflammation this damage cannot be repaired, which results in ongoing bacterial invasion and damage of the gut. As a result, these patients suffer from complications due to ongoing gut inflammation and need lifelong treatment.

In search for a treatment, we focused on understanding how the gut wall is kept intact at steady-state (also called 'homeostasis'). Here, we took a closer look at the locally produced hormone chromogranin A (**Fig. 1**). After production by specialized cells in the gut wall, chromogranin A is cut into six small active pieces; pancreastatin, WE-14, vasostatin, catestatin, chromofungin and serpinin. All these active pieces, which are called peptides, play a role in regulating health and disease.

Interestingly, the two peptides catestatin and pancreastatin seem to have opposing effects; where catestatin plays a role in suppressing inflammation and pancreastatin seems to stimulate inflammation. However, we do not currently know much about their function in controlling gut homeostasis. Therefore, we investigated the role of the active peptides catestatin and pancreastatin on the 'leaky' gut wall.

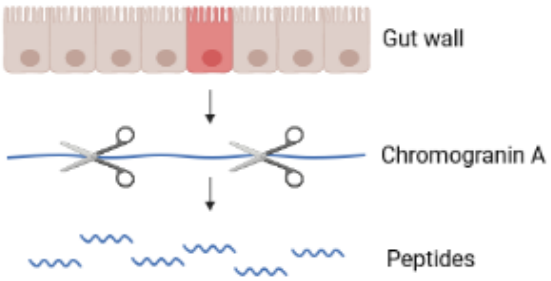

Fig. 1: Chromogranin A production and cutting resulting in the active peptides.

Findings
To be able to study the specific role of the complete hormone chromogranin A and its peptide catestatin in a physiological setting, we made so-called chromogranin A knockout (full hormone-KO) and catestatin knockout (peptide-KO) mice, meaning that we removed the genes that codes for the hormone or its peptide. The full hormone-KO mouse could no longer make chromogranin A, while the peptide-KO mouse could still make chromogranin A, but it could no longer cut it into the peptide catestatin. Additionally, we could feed normal or knockout mice a fluid containing only the full hormone or peptide to study its effect as a kind of medication. By using both mouse types and peptides as

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supplementation we could create specific situations necessary to study the role of chromogranin A and catestatin on the gut wall function.

First, we looked at the so called 'tight junctions', which are structures in the gut cells that keep them tightly together in one line (like the cells are holding hands). By using an ultrastructural microscope, that is able to enlarge even the most tiny structures inside the cells, we could see that the tight junctions in the peptide-KO mouse were longer and looked similar as in inflammatory bowel disease patients.

Secondly, we studied how 'leaky' the gut-wall was by measuring how much sugar made it to the other side of the gut-wall (the sugar was labelled with a green dye to be able to see it). Here, detection of green on the other side means 'leaky', because in a healthy situation the gut-wall is intact and we would not expect to detect green sugar on the other side. We learnt that the peptide catestatin is important for maintaining the gut barrier since the mice without catestatin showed a very 'leaky' gut. By treating the full hormone-KO mouse with either catestatin or pancreastatin, we could even see that the leakiness of the gut is oppositely regulated by these two peptides; meaning that in presence of catestatin the gut-wall seems intact, while after addition of pancreastatin the wall seems 'leaky'.

Thirdly, we identified the bacteria types present in the gut. In the peptide-KO mouse we found a higher amount of Firmicutes and a lower amount of Bacteroidetes than in the normal mouse. Normally, Firmicutes are necessary for energy uptake from food, whereas Bacteroidetes produce acids to keep a good environment in the gut for food uptake. However, these bacteria populations need to be balanced to be able to take up food and keep the gut in a steady-state. Interestingly, the same shift in bacteria groups we found in the peptide-KO mouse is also observed in inflammatory bowel disease patients. This shows us that the presence of catestatin is necessary to maintain a healthy balance in the gut bacteria that is present.

Finally, we measured that chromogranin A hormone and catestatin peptide levels in the blood of inflammatory bowel disease patients were elevated when compared to healthy people.

Conclusions

Altogether, the hormone chromogranin A and its active peptides play an important role in maintaining the gut wall function. Especially the peptide catestatin plays a role in making the gut wall less 'leaky' by affecting the length of the tight junction, the presence of bacteria, and the transport over the gut-wall barrier. Additionally, catestatin seems to exert its effect by opposing another peptide pancreastatin. Although we now know a great deal more about how these molecules affect gut homeostasis, more research is still necessary to define the exact working mechanism.

Our research is important to understand how gut homeostasis is regulated in health and disease. Additionally, blood catestatin levels might be used as a biomarker in the future to indicate the presence of inflammation in inflammatory bowel disease patients. Finally, catestatin and pancreastatin might be interesting in the future to develop treatments for inflammatory bowel disease and other gut-related diseases.

Article info

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