Medical & healthcare, Drug discovery

The tight junction protein occludin modulates blood–brain barrier integrity and neurological function after ischemic stroke in mice

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Abstract

The fundamental component of the physical barrier of the blood-brain barrier is the tight junction (TJ), which is an intercellular adhesion device of brain vascular endothelial cells. In addition to claudin-5 (Cldn5), occludin (Ocln), which belongs to the MARVEL family, is also present in abundance as a tight junction (TJ) protein of brain vascular endothelial cells. To investigate occludin's role, knockout (KO) mice were created. In these mice, cerebral infarction volume, extravascular permeability, neurological impairment, and mortality all increased compared to wild-type mice. Additionally, claudin-5 and ZO-1 expression was lower in Ocln KO mice. These findings suggest occludin is crucial for BBB integrity and neurological function after ischemic stroke.

Background & Results

Claudin-5 is uniformly expressed in brain endothelial cells forming the blood-brain barrier (BBB), but mice lacking claudin-5 show leakage of low molecular weight substances, indicating claudin-5 alone doesn't fully explain BBB breakdown after cerebral infarction. Although occludin (Ocln) is considered important for BBB function in vitro, in vivo evidence is limited, with Ocln knockout (KO) mice showing no major barrier issues under normal conditions. Thus, we generated Ocln KO mice to investigate Ocln's role in BBB integrity and neurofunction after cerebral infarction. In mice lacking Ocln, the size of the infarct area was larger than in wild-type mice, and there was an increase in extravascular permeability. Furthermore, neurological function was impaired, and mortality was increased. No significant difference in cerebral blood flow was observed between the two groups following cerebral infarction. Immunofluorescence staining revealed that the expression levels of Cldn-5 and ZO-1 were lower in Ocln KO mice than in WT mice, both in the infarcted and non-infarcted regions. Furthermore, an examination of extravascular leakage of FD-10 (molecular weight = 10 kDa) revealed that the leakage was greater in the KO than in the WT seven days after cerebral infarction. In physiological conditions, no difference was observed between WT and KO in terms of leakage of fluorescein, FD-4, and Sulfo-N-hydroxysulfosuccinimide-biotin. Furthermore, Ocln was found to play a role in the process of angiogenesis following cerebral infarction.

Significance of the research and Future perspective

This study indicate that Ocln exerts an influence on the BBB barrier function and neurological function following stroke. Furthermore, Ocln was identified as a factor influencing the expression level of Cldn5. The findings of this study indicate that regulating BBB function through gene transfer of Ocln or Cldn using adeno-associated virus (AAV) may offer a potential avenue for treating neurological disorders. Similarly, targeting TJ proteins could also be a promising approach for managing neurological disorders.

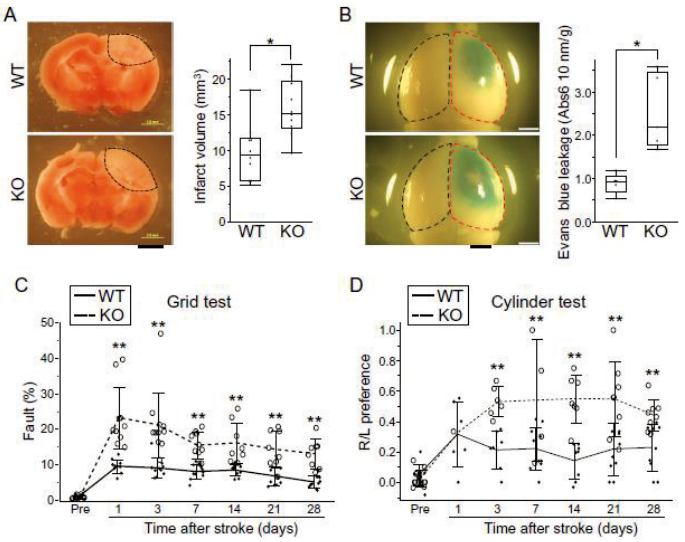

Figure1. Increased infarct size, increased permeability of the blood-brain barrier and worsened neurological function in occludin KO mice.

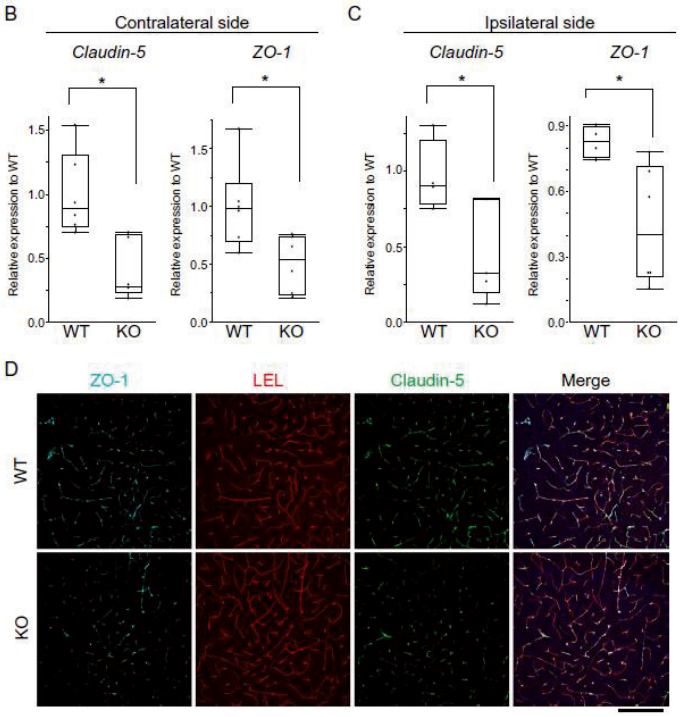

Figure2. In the Ocln KO model, the mRNA and protein expression levels of Cldn-5 and ZO-1 are observed to be lower than in the wild-type control.

Patent

Treatise
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URL

Keyword ischemic stroke, blood brain barrier, tight junction, occluding, claudin