Role of hypothalamic orexin system in prevention of nonalcoholic steatohepatitis (NASH) in obese mice

Hiroshi Tsuneki, Takahiro Maeda, Shinjiro Takata, Koyuki Otsuka, Kanta Kon, Tsutomu Wada, Sasaoka Toshiyasu

Dept. Clin. Pharmacol., Univ. of Toyama

Non-alcoholic steatohepatitis (NASH) is a severe form of fatty liver disease induced by obesity. So far, no therapeutic drug is available against NASH, because the pathogenic mechanism remains unclear. Since hypothalamic orexin system is a main regulator of energy homeostasis, we investigated the role of orexin against NASH under obese conditions, using orexin knockout (ORX-KO) mice fed high fat diet (HFD). ORX-KO mice showed severer obesity and glucose intolerance on HFD, compared to wild-type controls. Also, remarkable NASH-like phenotypes were observed in the liver of ORX-KO mice, such as the accumulation of triglyceride and the increase in the levels of biomarkers for endoplasmic reticulum (ER) stress (phosphorylation of eIF2α, etc.), chronic inflammation (Tnfα mRNA, etc.), and hepatic fibrosis (Tgfβ mRNA, etc.). When the HFD-fed ORX-KO mice were treated with orexin A (i.c.v.), the hepatic ER stress and chronic inflammation were improved, whereas body weight was not altered. These results indicate that the central action of orexin is required to prevent the development of NASH by reducing ER stress and chronic inflammation in the liver under the obese condition. Hypothalamic orexin system may be a crucial therapeutic target to promote the brain-liver network functions for preventing the progression of NASH.