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Professor Jin-Hee Ahn's research team opens up the possibility of developing a treatment for non-alcoholic fatty liver diseases

- Fatty liver, which is when the liver has more than 5% fat, has almost no symptoms. It progresses to cirrhosis of the liver or worsens the fatty liver, resulting in higher incidence of liver cancer. In particular, nonalcoholic fatty liver disease (NAFLD) is caused by obesity, diabetes, and metabolic syndrome, and is an increasing trend worldwide.
 - However, there is no drug approved as a treatment for nonalcoholic fatty liver disease, so it is urgent to develop a treatment.
- GIST (Gwangju Institute of Science and Technology, President Kiseon Kim) Department of Chemistry Professor Jin-Hee Ahn's research team developed a serotonin (5HT) receptor inhibitor (a substance that hinders the catalytic reaction of enzymes) in peripheral tissues, opening the possibility of developing a treatment for nonalcoholic fatty liver disease.
 - Serotonin is a well-known neurotransmitter for the central nervous system and is reported to be involved in maintaining energy homeostasis in peripheral tissues and regulates appetite.
 - When the research team administered a compound in a high-fat diet rat, it was confirmed that the weight of the liver decreased and the fat accumulation in

the liver decreased. Therefore, it is expected that future supplements can be used to treat nonalcoholic fatty liver disease.

□ Professor Jin-Hee Ahn's team wanted to find a new peripheral tissue-based compound from Pimavanserin, a known serotonin type 2 (5HT2A) inhibitor and a Parkinson's disease-related treatment approved by the FDA in 2016.

- As a result, the blood-brain barrier passage was reduced to mainly act on peripheral tissues and found a compound with excellent efficacy (IC₅₀ * = 8.35 nM). This compound has good microsomal stability in the liver and did not inhibit CYP ** and hERG ***. In addition, as a result of testing the medicinal effects for the other eight serotonin receptors, it was confirmed that 5HT2A was selectively inhibited.

* IC₅₀ (half maximal inhibitory concentration): concentration of a substance that inhibits certain biological or biochemical functions by 50%

** CYP (Cytochrome P): An enzyme that causes a one-phase drug metabolic reaction in the liver, which is very important for drug interaction and evaluation of efficacy and stability.

*** hERG (human Ether-a-go-go-Related Gene): If the heart has drug toxicity, it can induce delay of hERG potassium channel and cause heart disease such as arrhythmia.

- As a result of 10 weeks of animal testing of this compound in mice with a high fat diet, the fat accumulation in the liver and liver fat were mitigated, glucose tolerance * was improved, and the weight of the liver was reduced.

* glucose tolerance: the ability of cells to absorb glucose from the blood, used as a diagnosis of diabetes

□ Professor Jin-Hee Ahn said, "The results of this research are expected to be used for the development of new drugs in the future through the discovery of new targets for the treatment of nonalcoholic fatty liver disease and the development of therapeutic agents."

□ The research, conducted by GIST Professor Jin-Hee Ahn (corresponding author), was supported by the Ministry of Science and ICT and the Ministry of Health and Welfare. The article was published online on April 14, 2020 in the *Journal of Medicinal Chemistry*, a renowned international journal published in the field of medicinal chemistry by the American Chemistry Society.

