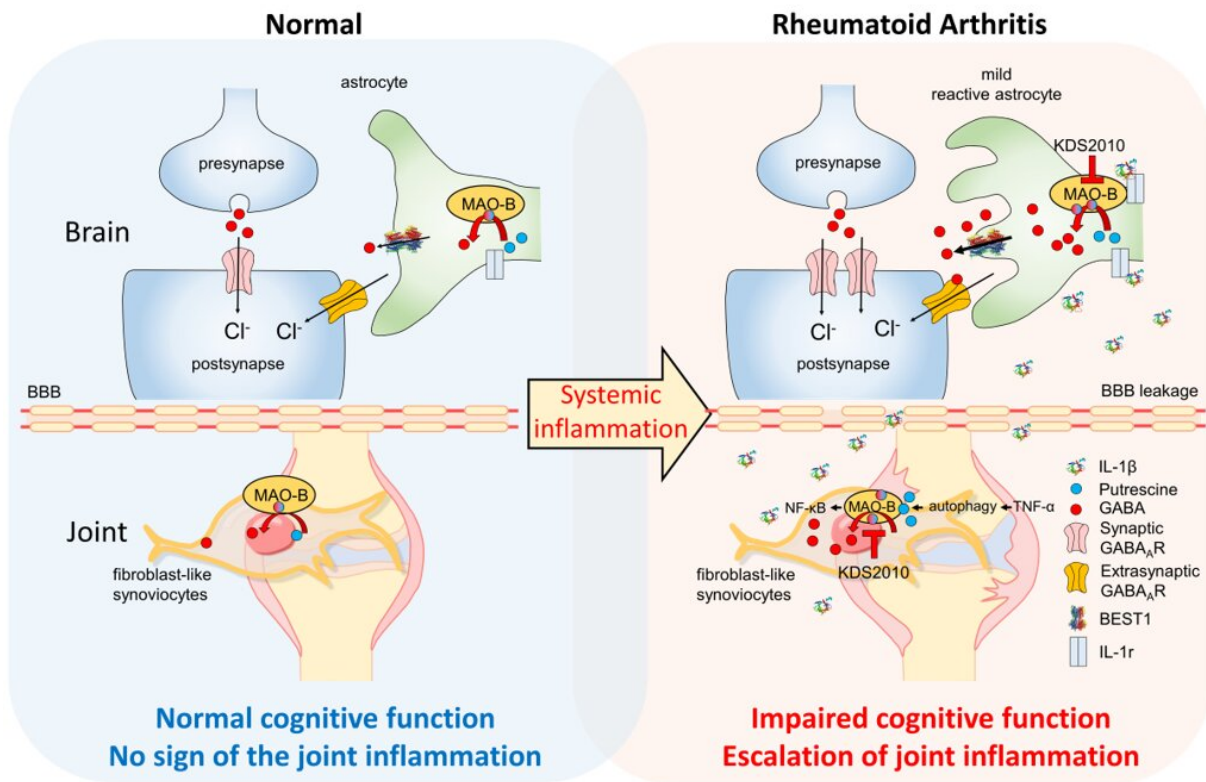


# Two birds one stone strategy to treat both joint pain and cognitive impairment in rheumatoid arthritis

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The inflammatory response of RA causes autophagy in FLSs to produce putrescine, which intensifies inflammation of GABA and H<sub>2</sub>O<sub>2</sub> through the MAO-B in the joint. In chronic inflammation, increased IL-1 $\beta$  passes through a loose blood-brain barrier and enters the brain. Increased IL-1 $\beta$  in the hippocampus causes cognitive impairment by activating astrocytes and by inhibiting synapse signaling by increasing the secretion of the inhibitory neurotransmitter GABA from MAO-B. Furthermore, the use of an MAO-B

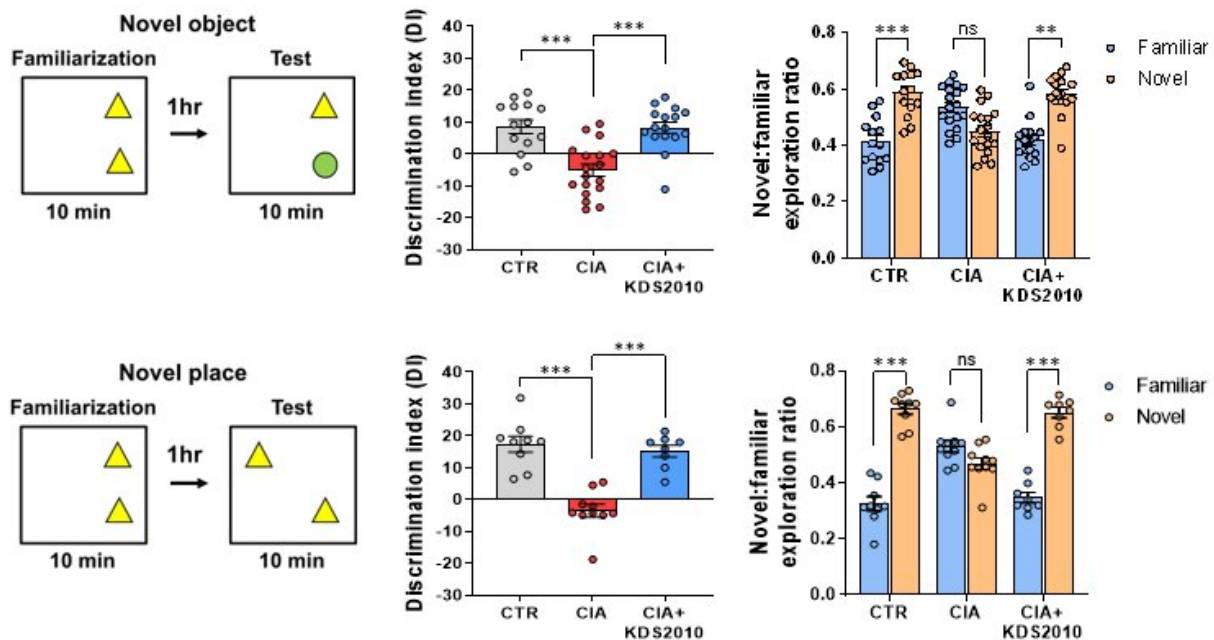
inhibitor can suppress the MAO-B of FLSs and astrocytes to relieve inflammation of the joints and alleviate cognitive function. Credit: Institute for Basic Science

Rheumatoid arthritis (RA) is an autoimmune disease that causes extensive inflammation of the joints, causing severe pain and discomfort in patients. But did you know that the disease is also commonly accompanied by neuropsychiatric complications, such as cognitive impairment and depression? Previous studies show that up to 70% of RA patients can have such cognitive disorders. These neurological symptoms are thought to be caused by neuroinflammation, which originates from systemic inflammation. However, the precise mechanisms of such cognitive impairment in RA remain unclear.

Previously, a team led by Director C. Justin LEE at the Center for Cognition and Sociality within the Institute for Basic Science (IBS) in Daejeon, South Korea, explored the hippocampus of dementia patients to better understand the overall mechanism of memory impairment. The group found that reactive astrocytes release an increased level of monoamine oxidase-B (MAO-B)-dependent gamma-aminobutyric acid (GABA), which in turn leads to neurological disorder.

MAOs, including MAO-A and MAO-B, are enzymes that catalyze the oxidation of monoamines and are bound to the outer mitochondrial membrane in cells of several organs, such as the brain and the immune system. More than 30 years ago, previous research suggested that MAO inhibitors can relieve pain and stiffness in RA patients. However, there have been no follow-up studies of these results, and further studies related to the role of MAO in RA have been generally lacking even until today.

Recently, Director Lee's team revealed that interleukin-1 $\beta$  (IL-1 $\beta$ ), one of these inflammatory substances that are responsible for RA, causes aberrant expression of MAO-B in fibroblast-like synoviocytes cells (FLSs) isolated from joint tissues of RA patients. It was revealed that both MAO-B and GABA are aberrantly expressed in these cells.



Behavioral experiments were conducted to evaluate the cognitive function of the RA animal model. RA animal model showed MAO-B-dependent cognitive impairment. Administration of KDS2010 restored cognitive function. Credit: Institute for Basic Science

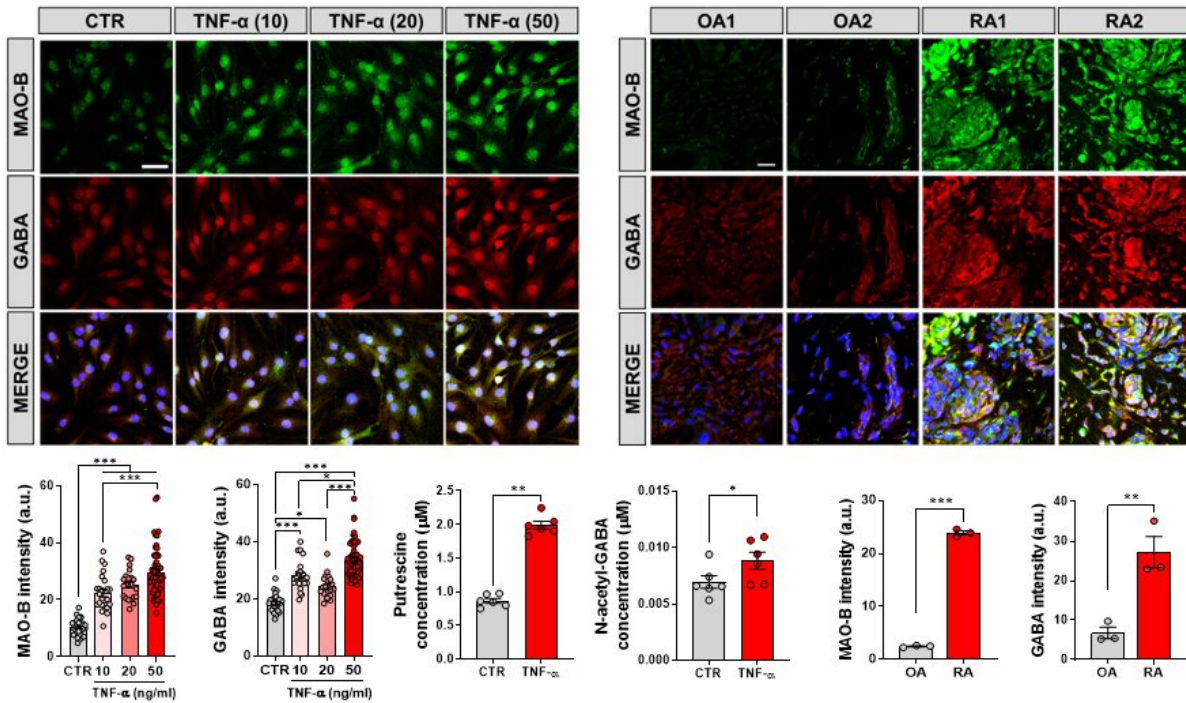
Published in *Experimental & Molecular Medicine*, the team's findings indicate that the expression of MAO-B and MAO-B products, such as GABA and H<sub>2</sub>O<sub>2</sub>, can exacerbate joint inflammation by upregulating the expression of proinflammatory factors. It was also observed that MAO-B and GABA levels were significantly increased in the RA tissue

compared to the osteoarthritis (OA) tissue, which generally has a lower level of inflammation.

Notably, the researcher also observed that the RA animal model showed increased [cognitive impairment](#). In routine behavioral experiments, normal healthy mice had no difficulty remembering a new object or location. On the other hand, it was shown that RA model mice were unable to distinguish new things and objects, which is a hallmark of a cognitive impairment disorder.

Similarly to the joint tissues, the secretion of astrocytic MAO-B-dependent GABA was aberrantly increased in the hippocampus, which is thought to be the main cause of this cognitive dysfunction. It has been known that hippocampal astrocytic MAO-B-mediated GABA inhibits neurons, causing memory and cognitive impairment. Based on the fact that astrocytes respond sensitively to inflammation, it was hypothesized that astrocytes would also be affected during the course of RA disease progression, which would lead to cognitive impairment.

The first author, Dr. WON Woojin states, "Until now, research on RA has focused only on the mechanism of inflammation, so the cause and treatment of cognitive impairment have not been clear. With a new approach of astrocytes and MAO-B, we were able to determine the cause of cognitive impairment."



MAO-B and GABA were found to be present in the joint fibroblast-like synoviocytes cells (FLSs), and the expression of MAO-B and GABA was associated with the degree of inflammation. Credit: Institute for Basic Science

Subsequently, the IBS researchers decided to administer an MAO-B inhibitor called "KSD2010" in the RA animal model. KDS2010 is a newly developed selective and reversible MAO-B inhibitor, which is currently being tested in phase 1 [clinical trials](#). Once administered in mice, it was discovered that both the joint inflammation decreased and cognitive function recovered at the same time.

Taken together, this study revealed both joint inflammation and cognitive impairment have a common underlying mechanism in RA patients, namely aberrant MAO-B expression. This opens the possibility of treating both of these symptoms with one drug.

"The mechanism by which cognitive impairment in RA is induced by reactive astrocytes caused by chronic [inflammation](#) was first presented. It is hoped that the newly developed and improved MAO-B inhibitor KDS2010 will become an effective next-generation treatment for RA," says Director C. Justin LEE, who supervised this work.

**More information:** Woojin Won et al, Inhibiting peripheral and central MAO-B ameliorates joint inflammation and cognitive impairment in rheumatoid arthritis, *Experimental & Molecular Medicine* (2022). [DOI: 10.1038/s12276-022-00830-z](https://doi.org/10.1038/s12276-022-00830-z)

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