1. No.

   2018T002

2. Title

   Nicotinic Acetylcholine Receptor as Target for Drug Discovery and Development
   - Involvement of Nicotinic Acetylcholine Receptor in the Pathophysiology of Stress- and Inflammation-induced Depression -

3. Period

   2018-2022

4. Summary

Using clinical and basic research, we elucidated the relationship between smoking and depression focusing on the tryptophan-kynurenine metabolic pathway and developed antidepressants that target nicotinic receptors. Clinical studies revealed that higher stress and depressive scores are related to higher smoking rates. Genome-Wide Association Study (GWAS) revealed that missense mutations in kynurenine aminotransferase 3 (KAT3) are associated with smoking behavior. We also showed that serum anthranilic acid (AA) is increased in patients with higher depressive scores. In basic research, we revealed that chronic unpredictable mild stress (CUMS) decreased kynurenine 3-monooxygenase (KMO) and Iba1 expression, a microglia marker, and increased kynurenic acid (KA) that has an α7 nicotinic acetylcholine receptor (α7nAChR) antagonist. These changes such as the decrease of KMO and Iba1 expression were due to the chronic elevation in serum corticosterone concentration by CUMS. CUMS increased serum AA by the supression of KMO expression in the liver. Moreover, nicotine, galantamine, an allosteric modulator of α7nAChR, and glycyrrhizic acid, a competitive inhibitor of KAT2, ameliorated the CUMS-induced decrease of social interaction time. Our clinical and basic research suggested that α7nAChR, a receptor antagonized by KA, and KAT, an enzyme synthesizing KA, are a potential drug target for depression.