

Knee Osteoarthritis-Induced Depression-Like Behavior in Mice and its Potential Link via the Kynurenine Pathway of Tryptophan Degradation

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ABSTRACT INTRODUCTION: Osteoarthritis (OA) is a prevalent chronic medical condition often accompanied by comorbid depression. The underlying pathophysiology linking OA and depression remains unclear, but previous investigations have suggested a role of persistent inflammation and activation of the kynurenine pathway of tryptophan degradation in this disease process. This study aimed to investigate whether OA could induce depressive-like behavior in mice and whether alterations in the tryptophan-kynurenine pathway were associated with the development of OA.

METHODS: Knee OA was induced in C57BL/6 mice (n=20) and sham surgeries were performed in control mice (n=20) (Figure 1A). OA was allowed to develop for either 6 (n=10) or 12 (n=10) weeks and was determined by the Osteoarthritis Histopathology Assessment System (Figure 1B-C). At 6 and 12 weeks, anxiety-like behavior was evaluated using the dark-light emergence test and depressive-like behavior was assessed using the forced swim and sucrose preference tests (Figure 1D-F). Kynurenine pathway metabolites were analyzed in synovial fluid, plasma, and the hippocampus after 12 weeks (Figure 2). IDO activity was quantified in the synovial fluid (SF), hippocampus, and plasma of OA and sham mice at 6 and 12 weeks (Figure 3A-D). Immunohistochemistry was used to examine protein expression of indoleamine 2,3-dioxygenase (IDO) and L-kynurenine at both 6 and 12 weeks (Figure 3E-F).

RESULTS SECTION: OA was confirmed histologically using the OARS1 scoring system. No anxiety-like behavior was observed in either group or time point. OA mice displayed significant depressive-like behavior, with prolonged immobility times in the forced swim test and decreased preference for sucrose at both 6 and 12 weeks. At 12 weeks post-surgery, both tryptophan and L-kynurenine were significantly elevated in the synovial fluid of OA animals. IDO activity was significantly elevated in the OA animals' plasma at 12 weeks. Immunohistochemistry revealed increased staining for both L-kynurenine and IDO in the synovium and remaining cartilage of OA animals at both time points.

DISCUSSION: The development of OA in mice led to significant depressive-like behavior and increases in the metabolites of the tryptophan-kynurenine pathway. These findings suggest a potential pathophysiological link between OA and depression, providing a basis for further research into therapeutic interventions targeting this pathway.

SIGNIFICANCE/CLINICAL RELEVANCE: These results support the concurrent development of depression-like behavior after induction of OA in a mouse model and partially implicate the tryptophan-kynurenine pathway in the development of comorbid depressive-like behaviors in mice with OA. Discovery of therapeutic interventions targeting this pathway could potentially mitigate concurrent development of depressive-like behaviors observed clinically amongst OA patients.

IMAGES AND TABLES:

