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論　文　内　容　の　要　旨
Synopsis of Thesis

氏　名 Name	HONORAT JOSEPHE ARCHIE オノラ　ジョセフ　アーチー
論文題名 Title	**Xanthine Oxidase Mediates Axonal and Myelin Loss in a Murine Model of Multiple Sclerosis**（キサンチンオキシダーゼ(XO)は多発性硬化症モデルの軸索及びミエリン障害を促進する）

論文内容の要旨

〔目　的(Purpose)〕

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, associated with demyelination and neurodegeneration. Although various mechanisms may contribute to tissue injury in MS, increasing evidence indicates that reactive oxygen species (ROS) play an important role in this process. Various pathways lead to ROS production; these include mitochondrial oxidative phosphorylation, oxidoreductase enzymes such as NADPH oxidase and xanthine oxidase (XO). XO is implicated in the pathogenesis of various pathological entities such as reperfusion injury and cardiovascular diseases through production of ROS. In this study, we investigated the role of XO in the pathophysiology of MS lesions in order to develop a potent new therapy for MS based on XO inhibition.

〔方法ならびに成績(Methods/Results)〕

Methods: Experimental autoimmune encephalomyelitis (EAE), a murine model of MS, was used. SJL/J mice which develop a relapsing-remitting EAE, was utilized to assess the expression and the activity of XO in EAE. These mice were also used to investigate the effects of a selective XO inhibitor, febuxostat, on the clinical course of the disease, on glial cells activation and on oxidative damage. NOD/ShiJcl mice were used to investigate the effects of febuxostat on axonal and neuronal damage of secondary progressive EAE. GMI-M6-3 microglia and J774 macrophage cell lines were used to study the effects of febuxostat on ROS production in vitro.

Results: We found that XO was highly expressed in the central nervous system (CNS) of EAE mice, while almost no expression was detected in the naïve mice. The cells expressing XO were predominantly infiltrating macrophages and activated microglia. XO activity was increased in serum and CNS of EAE mice compared to naïve mice. EAE mice treated prophylactically with febuxostat, showed decreased activity of XO, reduced oxidative stress and significant amelioration of their clinical score compared to non-treated mice. Febuxostat also decreased inflammatory cells infiltration into the CNS and reduced the activation of astrocytes and microglia the CNS parenchyma but had no effects on the activation of peripheral immune system. Moreover, febuxostat inhibits the expression of XO in macrophages and microglia in vitro and decreased ROS production by those cells. Therapeutic administration of febuxostat also ameliorated the severity of the clinical score of EAE and decreased the relapse rate in the treated mice. In addition, febuxostat significantly reduced the progression of the disease in secondary progressive EAE. The treated mice showed less severe axonal loss and demyelination compared to the control group.

〔総　括(Conclusion)〕

These results highlight the implication of XO in EAE pathogenesis and suggest XO as a target for MS treatment and febuxostat as a promising therapeutic option for MS patients.

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論文審査の結果の要旨及び担当者

（申請者氏名） **Honorat Josephe Archie**

論文審査担当者	（職）	氏名
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論文審査の結果の要旨

中枢神経系の炎症性脱髄疾患である多発性硬化症の病態に活性酸素種（ROS）が関与していることが示唆されていた。ROSの産生経路についてはNADPHオキシダーゼやキサンチンオキシダーゼ（XO）などいくつかの酵素の関与が推測されるが、XOについてはほとんど報告が無かった。

本研究では多発性硬化症のモデル動物である実験的自己免疫性脳脊髄炎（EAE）マウスを利用し、中枢神経組織でXOが著明に発現亢進していることを免疫組織学的に示し、XO活性も亢進していることを初めて示した。さらに選択的XO阻害剤であるフェブキソスタットの投与によりXO活性およびROS産生が抑制されEAEの症状が軽症化することを示した。本研究は、XOが多発性硬化症の治療標的になることを示したことと同時に、フェブキソスタットは高尿酸血症治療薬として承認されている安全な薬剤であり、ヒト多発性硬化症への応用も可能であることをも示した意義がある。

以上のことから本研究は、学位の授与に値すると考えられる。