様式３

論　文　内　容　の　要　旨

氏　名　（　藤井　雄太　）	
論文題名	Investigation of novel safety biomarker for arteritis using in vivo MRI (in vivo MRIを用いた動脈炎の新規安全性バイオマーカーの探索)

Since drug-induced arteritis is difficult to monitor in clinical trials, the occurrence of arteritis in nonclinical toxicological studies of a candidate drug makes development of the drug very difficult. Although arteritis is a severe toxicity, the lesion is completely recovered if the offending drug is discontinued or treatment is initiated at an early phase. If arteritis can be detected in an early phase with a biomarker, clinical trials can be conducted safely. Therefore, biomarker for identifying drug-induced arteritis is highly desirable. Since evaluation in humans is difficult, firstly I conducted the research with rats. On magnetic resonance imaging (MRI) in rodents, evaluation of the organs requires higher resolution due to their small size, and research had not progressed as same as in human. However, in vivo imaging techniques, including MRI in rodents, have made remarkable advances in recent years.

I made hypothesis that MRI could be used to find a biomarker candidate for drug-induced arteritis. However, there are no reports on the evaluation of drug-induced arteritis by MRI. Therefore, I conducted this study to clarify whether the finding by MRI can be a biomarker as follows.

First study was conducted to clarify which dosing regimen was appropriate for MRI assessment. Based on the obtained results, subcutaneously administered once daily 100 mg/kg/day in FM and 40 mg/kg/day in MH for 2 days is considered an optimal dosing regimen for MRI assessment.

The second study was conducted to clarify whether fenoldopam mesylate (FM)-induced arteritis in rats can be detected by MRI. FM causes arteritis due to its vasodilatory effect. Mesenteric arteries were examined with ex vivo high-resolution MRI, postmortem MRI and in vivo MRI on the day after final dosing or 3 days after administration of the final dose. The ex vivo MRI showed low-intensity areas and a high signal intensity region around the artery, and these findings were considered to be erythrocytes infiltrating the arterial wall and perivascular edema, respectively. In the in vivo study, the MRI of the FM-administered group showed a high signal intensity region around the artery.

The third study was conducted to clarify whether arteritis induced by vasoconstrictor effect could be detected by MRI. The mesenteric arteries of midodrine hydrochloride (MH)-administered animals were examined using in vivo MRI at 1 day or 7 days after administration of the final dose. High signal intensity region around the artery was observed in animals with minimal perivascular lesions and not observed in an animal without histological changes on the day after the final dose. On the 7th day after the final dose, no abnormality was observed in histopathological examinations and no high signal intensity regions were observed by MRI in any animal.

In conclusion, our results indicated that regardless of pathogenic mechanism and degree of changes, high signal intensity region in MRI could be a versatile biomarker for detecting the arteritis with high specificity and high sensitivity. In addition, it is suggested it could be possible to judge the discontinuation of administration of a drug in the phase of minimal lesion, which can be completely resolved. This is extremely useful for conducting clinical trials of drugs that may cause arteritis.

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論文審査の結果の要旨及び担当者

氏　名（　藤井　雄太　）		
	(職)	氏　名
論文審査担当者		
主 査	教授	八木 健
副 査	教授	髙島 成二
副 査	教授	上田 昌宏
副 査	教授	井上 豪

論文審査の結果の要旨

薬剤性血管炎は、バイオマーカーがないため、医薬品開発での大きな問題となっている。課題への取り組みの第一歩として、ラットにおける動脈炎に対する新規バイオマーカーの探索を行った。異なるメカニズムにより生じる2つの薬剤性血管炎モデルを用いた検討を行い、MRIによる動脈周囲の高信号化がバイオマーカーになりうることを見出した。本手法は、軽微な変化であっても検出可能であり、汎用性のある手法であることを明らかにし、特異的で鋭敏なバイオマーカーになりうることを見出した。本論文における薬剤性動脈炎の検出はヒトや動物を含め、これまでに報告がなく、また、ラットにおいて小型の動脈炎をMRIにて評価・検出した研究成果は世界初のものであり、博士の学位を授与するに値するものと認める。なお、チェックツール“iThenticate”を使用し、剽窃、引用漏れ、二重投稿等のチェックを終えていることを申し添えます。