（様式３号）

学　位　論　文　の　要　旨

氏名 路 倩

〔題名〕 Hesperetin inhibits sphingosylphosphorylcholine-induced vascular smooth muscle contraction by regulating the Fyn/Rho-kinase pathway

（ヘスペレチンは、Fyn / Rho キナーゼ経路を調節することにより、スフィンゴシルホスホリルコリン誘発性の血管平滑筋収縮を阻害する）

〔要旨〕

Cardiovascular diseases are the leading cause of mortality and disability worldwide. We have previously found that sphingosylphosphorylcholine (SPC) is the key molecule leading to vasospasm. We have also identified the SPC/Src family protein tyrosine kinase Fyn/Rho-kinase (ROK) pathway as a novel signaling pathway for Ca^{2+}-sensitization of vascular smooth muscle (VSM) contraction. The present study aimed to investigate whether hesperetin can inhibit the SPC-induced contraction with little effect on 40 mM K^{+}-induced Ca^{2+}-dependent contraction and to elucidate the underlying mechanisms. Hesperetin significantly inhibited the SPC-induced contraction of porcine coronary artery smooth muscle strips with little effect on 40 mM K^{+}-induced contraction. Hesperetin blocked the SPC-induced translocation of Fyn and ROK from the cytosol to the membrane in human coronary artery smooth muscle cells (HCASMCs). SPC decreased the phosphorylation level of Fyn at Y531 in both VSMs and HCASMCs and increased the phosphorylation levels of Fyn at Y420, myosin phosphatase target subunit 1 (MYPT1) at T853 and myosin light chain (MLC) at S19 in both VSMs and HCASMCs, which were significantly suppressed by hesperetin. Our results indicate that hesperetin inhibits the SPC-induced contraction at least in part by suppressing the Fyn/ROK pathway, suggesting that hesperetin can be a novel drug to prevent and treat vasospasm.

作成要領
１．要旨は、８００字以内で、１枚でまとめること。
２．題名は、和訳を括弧書きで記載すること。

(様式９号)

学位論文審査の結果の要旨

令和　4年　2月　17日

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学位論文題目名 (題目名が英文の場合、行を変えて和訳を括弧書きで記載する。)

Hesperetin inhibits sphingosylphosphorylcholine-induced vascular smooth muscle contraction by regulating the Fyn/Rho-kinase pathway

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学位論文の関連論文題目名 (題目名が英文の場合、行を変えて和訳を括弧書きで記載する。)

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Cardiovascular diseases are the leading cause of mortality and disability worldwide. It was previously found that sphingosylphosphorylcholine (SPC) is the key molecule leading to vasospasm, and identified the SPC/Src family protein tyrosine kinase Fyn/Rho-kinase (ROK) pathway as a novel signaling pathway for Ca^{2+}-sensitization of vascular smooth muscle (VSM) contraction. The present study aimed to investigate whether hesperetin can inhibit the SPC-induced contraction with little effect on 40 mM K^+-induced Ca^{2+}-dependent contraction and to elucidate the underlying mechanisms. Hesperetin significantly inhibited the SPC-induced contraction of porcine coronary artery smooth muscle strips with little effect on 40 mM K^+-induced contraction. Hesperetin blocked the SPC-induced translocation of Fyn and ROK from the cytosol to the membrane in human coronary artery smooth muscle cells (HCASMCs). SPC decreased the phosphorylation level of Fyn at Y531 in both VSMs and HCASMCs and increased the phosphorylation levels of Fyn at Y420, myosin phosphatase target subunit 1 (MYPT1) at T853 and myosin light chain (MLC) at S19 in both VSMs and HCASMCs, which were significantly suppressed by hesperetin. These results indicated that hesperetin inhibits the SPC-induced contraction at least in part by suppressing the Fyn/ROK pathway, suggesting that hesperetin can be a novel drug to prevent and treat vasospasm.

本論文は、ヘスペレチンがFyn/Rho キナーゼ経路を遮断する事により、スフィンゴシルホスホリルコリンによるCa^{2+}非依存性血管平滑筋収縮を抑制する事を解明したものであり、学位論文として価値あるものと認めた。

備考　審査の要旨は８００字以内とすること。