

(様式 3 号)

学 位 論 文 の 要 旨

氏名 Li Nan

〔題名〕

Inhibitory effects of tangeretin on the sphingosylphosphorylcholine (SPC)-induced vascular smooth muscle contraction through suppressing the Fyn/Rho-kinase signaling pathway
(Fyn/Rho-キナーゼシグナル伝達経路の抑制を介したスフィンゴシルホスホリルコリン (SPC) 誘発血管平滑筋収縮に対するタンゲレチンの阻害効果)

〔要旨〕

We previously discovered that the SPC/Fyn/Rho-kinase (ROK) pathway mediates the Ca^{2+} -sensitization of vascular smooth muscle (VSM) contraction leading to vasospasm, a major cause of sudden death. Lately, we have been trying to find and develop more natural edible compounds which can treat and/or prevent the SPC-induced abnormal VSM contraction, and finally found that tangeretin (5, 6, 7, 8, 4'-pentamethoxyflavone), a natural compound extracted from citrus plants, can inhibit the SPC-induced VSM contraction of porcine coronary arteries both in the pretreatment and posttreatment. However, the underlying molecular mechanism(s) has not been clarified yet. In this study, we aimed to clarify the molecular mechanism(s) by which tangeretin inhibits the SPC-induced abnormal VSM contraction. In VSM tissues of porcine coronary arteries, tangeretin showed remarkable inhibitory effects on the SPC-induced contraction with modest inhibitory effects on the high K^{+} -depolarization-induced Ca^{2+} -dependent contraction, both in pretreatment and posttreatment at the optimal concentrations; In cultured VSM cells, tangeretin can also abolish the SPC-induced cell contraction. Regarding the mechanisms, tangeretin markedly inhibited the SPC-induced activation of Fyn and ROK; the immunocytochemical analysis demonstrated that tangeretin inhibited the SPC-induced the translocation of Fyn and ROK from the cytoplasm to the cell membrane, resulting in the reduction of phosphorylation of myosin light chain. Taken together, these findings indicate that tangeretin, upon pre- or post-treatment, inhibits the SPC-induced VSM contraction through suppressing the Fyn/ROK signaling pathway, thereby suggesting that tangeretin can be a potential candidate for the treatment and/or prevention of 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。

学位論文審査の結果の要旨

令和4年8月1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。) Inhibitory effects of tangeretin on the sphingosylphosphorylcholine (SPC)-induced vascular smooth muscle contraction through suppressing the Fyn/Rho-kinase signaling pathway (Fyn / Rho-キナーゼシグナル伝達経路の抑制を介したスフィンゴシルホスホリルコリン (SPC) 誘発血管平滑筋収縮に対するタンゲレチンの阻害効果) | | | |
| 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。) Inhibitory mechanism of tangeretin, a citrus flavone on the sphingosylphosphorylcholine (SPC)-induced vascular smooth muscle contraction (スフィンゴシルホスホリルコリン (SPC) 誘発性血管平滑筋収縮に対する柑橘類フラボンであるタンゲレチンの阻害機構) 掲載雑誌名 Journal of Pharmacological Sciences 第149巻 第4号 P.189~197 (2022年8月 掲載・ 掲載予定) 著者 (全員を記載) Nan Li, Ying Zhang, Tomoka Morita, Hiroko Kishi, Sei Kobayashi | | | |
| (論文審査の要旨) It was previously reported that the sphingosylphosphorylcholine (SPC)/Fyn/Rho-kinase (ROK) pathway mediates the Ca^{2+} -sensitization of coronary arterial smooth muscle (CASM) contraction leading to vasospasm, a major cause of sudden death. In this study, I attempted to find and develop more natural edible compounds which can treat and/or prevent the SPC-induced abnormal CASM contraction, and then discovered that tangeretin (5,6,7,8,4'-pentamethoxyflavone), a natural compound extracted from citrus plants, can inhibit the SPC-induced CASM contraction both in the pretreatment and posttreatment. In porcine CASM tissues, tangeretin showed remarkable inhibitory effects on the SPC-induced contraction with modest inhibitory effects on the high K^{+} -depolarization-induced Ca^{2+} -dependent contraction, both in pretreatment and posttreatment at the optimal concentrations; Regarding the mechanisms, tangeretin markedly abolished the SPC-induced cell contraction through inhibiting the SPC-induced activation and translocation of Fyn and ROK from the cytoplasm to the cell membrane in cultured CASM cells, resulting in the reduction of phosphorylation of myosin light chain. Taken together, these findings indicate that tangeretin, upon pre- or post-treatment, inhibits the SPC-induced CASM contraction through suppressing the Fyn/ROK signaling pathway, thereby suggesting that tangeretin can be a potential candidate for the treatment and/or prevention of vasospasm. | | | |
| 本論文は、タンゲレチンがFyn/Rho キナーゼシグナル伝達経路の抑制を介して、スフィンゴシルホスホリルコリン誘発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 | | | |