

(様式3号)

学位論文の要旨

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〔題名〕

Madagascine activates AMPK to induce vasodilatation
(Madagascine は AMPK を活性化して血管拡張を誘発する)

〔要旨〕

BACKGROUND AND PURPOSE

Madagascine (3-isopentenylxyemodin), is found to have more potent biological activities than the parent compound emodin. Madagascine can be chemically synthesized or purified from several *Rhamnus* species. This study was designed to characterize the effects of madagascine on activation of AMP-activated protein kinase (AMPK) induced vasodilatation.

EXPERIMENTAL APPROACH

The effects of madagascine on vasoconstriction induced by K^+ and on Ca^{2+} -independent vasoconstriction induced by sphingosylphosphorylcholine (SPC) which has a pivotal role in vasospasm were studied. The contractile force and intracellular Ca^{2+} were respectively studied using a fura-2 fluorometer. The potential mechanism was studied using endothelial cells and vascular smooth muscle (VSM) cells respectively.

KEY RESULTS

The constriction of isolated rat mesenteric resistance arteries with intact endothelium induced by 40 mM K^+ was significantly inhibited by madagascine (0.3-100 μ M) and the inhibition was abolished by epithelial nitric oxide synthase (eNOS) inhibitor L-NAME and AMPK inhibitor compound C. Madagascine also significantly inhibited the constriction of porcine VSM induced by SPC and the inhibition was also abolished by compound C. Madagascine significantly increased the phosphorylation of eNOS in endothelial cells while decreasing the phosphorylation of myosin phosphatase target subunit 1 (MYPT1) in HCASMCs. These madagascine-induced regulatory effects were abrogated using small interfering RNA knockdown of AMPK.

CONCLUSIONS AND IMPLICATIONS

Madagascine exerted vasodilatation through activating AMPK, leading to the activation of eNOS in epithelium and inhibition of ROCK/MYPT1 in VSM. This study suggests the potential value of madagascine in amelioration of hypertension and 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

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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。) Madagascine activates AMPK to induce vasodilatation (Madagascine は AMPK を活性化して血管拡張を誘発する) | | | |
| 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。) Madagascine induces vasodilatation via activation of AMPK (Madagascine は AMPK の活性化を介して血管拡張を誘発する) 掲載雑誌名 Frontiers in Pharmacology 第 7 巻 第 435 号 P.1 ~ 12 (2016 年 11 月 掲載 掲載予定) | | | |
| (論文審査の要旨) BACKGROUND AND PURPOSE Madagascine (3-isopentenylxyemodin), is found to have more potent biological activities than the parent compound emodin. Madagascine can be chemically synthesized or purified from several Rhamnus species. This study was designed to characterize the effects of madagascine on activation of AMP-activated protein kinase (AMPK) induced vasodilatation. EXPERIMENTAL APPROACH The effects of madagascine on vasoconstriction induced by K ⁺ and on Ca ²⁺ -independent vasoconstriction induced by sphingosylphosphorylcholine (SPC) which has a pivotal role in vasospasm were studied. The contractile force and intracellular Ca ²⁺ were respectively studied using a fura-2 fluorometer. The potential mechanism was studied using endothelial cells and vascular smooth muscle (VSM) cells respectively. KEY RESULTS The constriction of isolated rat mesenteric resistance arteries with intact endothelium induced by 40 mM K ⁺ was significantly inhibited by madagascine (0.3-100μM) and the inhibition was abolished by epithelial nitric oxide synthase (eNOS) inhibitor L-NAME and AMPK inhibitor compound C. Madagascine also significantly inhibited the constriction of porcine VSM induced by SPC and the inhibition was also abolished by compound C. Madagascine significantly increased the phosphorylation of eNOS in endothelial cells while decreasing the phosphorylation of myosin phosphatase target subunit 1 (MYPT1) in HCASMCs. These madagascine-induced regulatory effects were abrogated using small interfering RNA knockdown of AMPK. CONCLUSIONS AND IMPLICATIONS Madagascine exerted vasodilatation through activating AMPK, leading to the activation of eNOS in epithelium and inhibition of ROCK/MYPT1 in VSM. This study suggests the potential value of madagascine in amelioration of hypertension and vasospasm. 本論文は、Madagascine が AMPK 経路を介した血管内皮および血管平滑筋への作用を確認したものであり、学位論文として価値あるものと認めた。 | | | |