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Development of non-peptide type of angiotensin II type 1 receptor ligand as a biased agonist

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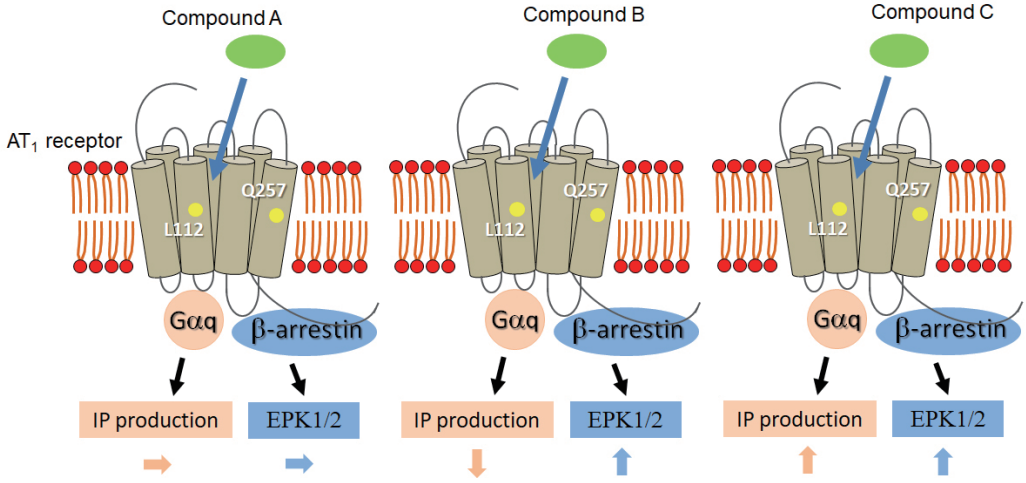
Objective: Peptide type of angiotensin II (Ang II) type 1 (AT1) receptor ligand as a biased agonist antagonized Ang II-stimulated G protein signaling, but stimulated several kinase pathways. Here, we developed non-peptide type of AT1 receptor compound as a biased ligand.

Design and method: We synthesized three non-peptide type of AT1 receptor ligands (Compound A, B and C) as candidates of biased ligands. These compounds were provided by Daiichi Sankyo Co. LTD. In vitro studies, inositol phosphate (IP) production and extracellular signal-regulated kinase (ERK) 1/2 activation were measured using AT1 receptor overexpressing cell system. We mutated the AT1 receptor (L112A, Q257A, Y292A and N295A receptors) and examined binding modes of receptor-ligand by competition binding study, and subsequently analyzed whether these ligands would induce IP production and ERK1/2 activation.

Results: Kd of Compound A, B and C to AT1 wild-type receptor by competition binding study were 0.8, 21 and 48 nM, respectively. Kd of Compound A, B and C to L112A receptor were 37, 23 and 31 nM, respectively. Compound B and C decreased and increased IP production, respectively, whereas Compound A did not change IP production. Compound B and C, but not Compound A, activated ERK1/2. L112A had a key role of IP production.

Conclusions: Compound A, B and C were a neutral antagonist, an inverse agonist, and an agonist with regard to IP production, respectively. On the other hand, Compound B and C, but not Compound A, were agonists to ERK1/2 activation. Thus, we developed non-peptide type of AT1 receptor compound as a biased ligand.

アンジオテンシンⅡ（Ang Ⅱ）タイプⅠ（AT1）受容体拮抗薬（ARB）は、降圧薬・心保護薬として広く処方されています。ARB は、Ang II の刺激を阻害し降圧を発揮する G protein 経路阻害に加えて、抗アポトーシス作用を示すβ-arrestin 経路も阻害するため、抗がん剤による心筋障害の抑制薬としては不適切です。理想的な治療薬は、G protein 経路は阻害し、β-arrestin 経路を作動するβ-arrestin-biased orthosteric ligand です。私たちは、新規非ペプチド型 AT1 受容体選択的作動薬（Biased ligand）の候補を見出しました。今後は、基礎研究により検証された結果を臨床に活かせるように薬剤開発を目指したいと思います。



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Association between major adverse cardiovascular events and Gensini score in hypertensive patients who underwent coronary computed tomography angiography

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Objective: From the Fukuoka University coronary computed tomography angiography (FU-CCTA) registry, we present major cardiovascular events (MACEs) in hypertensive patients who underwent CCTA, and the association between MACE and Gensini score of coronary arteries.

Design and method: Of the patients who underwent CCTA for the purpose of screening for CAD at Fukuoka University Hospital (FU-CCTA registry), 318 hypertensive patients with suspected CAD or at least one cardiovascular risk factor were enrolled. A severity of atherosclerosis of coronary arteries was assessed by the Gensini score. The coronary artery calcification score (CACS) was defined as the presence of two or more contiguous pixels with more than 130 Hounsfield Units on CT images at the time of CCTA. MACEs (all-cause death, ischemic stroke, acute myocardial infarction, coronary revascularization) was a primary endpoint for the follow-up of patients for up to 5 years. The patients were divided into two groups according to the presence (MACEs group) or absence (non-MACEs group) of MACEs.

Results: The average age was 68 ± 10 years and 50 % were males. The percentages of smoking, dyslipidemia, diabetes and chronic kidney disease were 37 %, 70 %, 26 % and 35 %, respectively. The P %males, %smoking, CACS and Gensini score in the MACEs group were significantly higher than that in the non-MACEs group, whereas there were no differences in age, dyslipidemia, diabetes and chronic kidney disease between the groups. Regarding the relationships between MACEs and various coronary risk factors, CACS or Gensini score by a Cox regression analysis, significant relationships were observed for the CACS (=0.019) and the Gensini score (= 0.002).

Conclusions: CACS or Gensini score could be a predictor of MACEs in hypertensive patients who underwent CCTA.

高血圧は、冠動脈疾患発症リスクの中でも重要な疾患です。今回は、高血圧患者に限定し、MACE の予測因子として CACS や Gensini score が重要であることを報告しました。

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