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Sub Title	
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Publisher	共立薬科大学
Publication year	1987
Jtitle	共立薬科大学研究年報 (The annual report of the Kyoritsu College of Pharmacy). No.32 (1987.) ,p.53- 54
JaLC DOI	
Abstract	
Notes	抄録
Genre	Technical Report
URL	https://koara.lib.keio.ac.jp/xoonips/modules/xoonips/detail.php?koara_id=AN00062898-00000032-0053

Some Unique Feature of the Metabolic Conversion of Platelet-Activating Factor (AGEPC) to Alkyl Acyl PC by Washed Rabbit Platelets*

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AGEPC (Platelet-activating factor) is a unique phospholipid chemical mediator with a chemical structure of 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine which exhibits a potent biological activity toward a number of cell types as well as tissues. The metabolism of this bioactive phospholipid has been investigated in plasma, in intact cells and *in vivo*. The pathway and mechanism of this metabolism, however is not well defined.

Recently several synthetic analogs of 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine (AGEPC ; platelet-activating factor) were characterized as selective inhibitors of this agonist's effects on rabbit platelets (TOKUMURA A., HOMMA H. & HANAHAN D.J., J. Biol. Chem. **260** (1985) 12710—12714). In this current investigation, these studies have been extended to include a further inquiry into the biochemical nature of the metabolic inactivation of AGEPC in rabbit platelets, and the effect of these analogs on this process. The inhibitors of AGEPC biological activity on rabbit platelets (U 66985 or CV 3988) blocked the metabolism of AGEPC, as reflected in the production of 1-*O*--alkyl-2-(lyso)-*sn*-glycero-3-phosphocholine (lyso GEPC) as well as 1-*O*-alkyl-2-acyl-*sn*-glycero-3-phosphocholine (alkyl acyl PC). The metabolic conversion of AGEPC to alkyl acyl PC was inhibited apparently seven fold by the most potent analog, U 66985. On the other hand, those analogs with low (U 68043) or no biological inhibitory activity (lysoGEPC) had marginal effects on the metabolism of AGEPC. This inhibitory effects of the inhibitors on the metabolism of AGEPC was not simply due to the competitive inhibition of the inhibitors on the metabolic sequence of AGEPC. In platelets which had been pretreated with AGEPC in absence of extracellular Ca^{2+} (desensitized) and washed, the metabolic conversion of AGEPC to alkyl acyl PC was actually enhanced. Thus metabolic inactivation of AGEPC was shown to be self-stimulated and persist in activated cells. This enhancement of metabolic inactivation of AGEPC was also observed upon the activation of the cells with thrombin, collagen or ionophore A 23187, indicating that the metabolism of AGEPC was enhanced upon the activation of the cells by AGEPC as well as other agonists.

Nearly 85% of the fatty acyl residues was arachidonate in the alkyl acyl PC derived from AGEPC. This specific acylation with arachidonate was observed regardless of the

* 本報告は*Arch. Biochem. Biophys.*, **252**, 259—268 (1987) に発表.

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presence of the inhibitor and in the desensitized cells, indicating that selectivity for arachidonate is not dependent on the enhancement of the metabolism of AGEPC. The alkyl acyl PC in the activated cells by thrombin, collagen or A 23187 was also predominantly alkyl arachidonoyl PC. The exact distribution of fatty acyl residues were, however different in each instance.

Thus it was shown that the inactivation of AGEPC by its conversion to alkyl acyl PC by rabbit platelets is enhanced by AGEPC itself and that excess amounts of AGEPC could be further inactivated by the enhanced capacity of the metabolism.