ヒト炭酸脱水酵素Ⅰ及びⅡに対する ラタノプロスト遊離酸の阻害機構

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The Mechanisms by which Latanoprost Free Acid Inhibits Human Carbonic Anhydrase I and II

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ABSTRACT Latanoprost, a prostaglandin F2alpha analogue, has been shown to be an effective ocular hypotensive agent when used alone on ocular hypertensive or open angle glaucoma patients. Another type of drugs, carbonic anhydrase inhibitors, are used to reduce ocular hypertension by decreasing aqueous humor secretion, and given in combination with prostaglandin F2alpha analogue. Another prostaglandin F2alpha analogue, Minprostin F_{2a}, has been shown to increase the CA activity and blood pressure. However, effects Latanoprost on CA have not been studied. Therefore, we studied effects of latanoprost free acid on human carbonic anhydrase (HCA) I and II using the stopped flow method.

Latanoprost free acid inhibited the hydration activity of HCA I or II by a noncompetitive mechanism. The inhibition constants (*Ki*) of latanoprost free acid for HCA I and II were respectively 0.22 and 2.3 mM in 0.05 M imidazole buffer at pH 7.4 (I=0.1). Therefore, latanoprost free acid is a weak inhibitor of HCA I or II. AutoDock simulation of the latanoprost free acid-HCA I or II complex showed that the carboxylic moiety of latanoprost free acid, which is located at the end of the molecule, binds to the zinc ion of the active site according to the stretching of the chain of latanoprost free acid through the narrow and deep active site cavity of HCA I or II. The inhibition mechanism of latanoprost free acid is shown to be very similar to that of the simple anions which bind to the zinc ion in the active site by the AutoDock simulation.

抄録　緑内障治療薬であるラタノプロストは遊離型で、ヒト炭酸脱水酵素Ⅰ及びⅡを非拮抗型阻害機構で阻害することを明らかにした。AutoDocking法で遊離ラタノプロストの結合部位を探査した結果、ラタノプロストは酵素の活性部位の亜鉛に結合して阻害することが判明した。この事は酵素活性阻害より得られた阻害機構と全く一致した。

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