チモロールは人炭酸脱水酵素Ⅰ及びⅡの酵素活性を活性化する。

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Timolol Activates the Enzyme Activities of Human Carbonic Anhydrase Ⅰ and Ⅱ.

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ABSTRACT: Timolol, a beta-blocker, has been shown to be an effective ocular hypotensive agent when used alone or with carbonic anhydrase inhibitor on ocular hypertensive or open angle glaucoma patients. The effect of timolol hemihydrate on the CO2 hydration activities of human carbonic anhydrase (HCA) I and II and its reaction mechanism were investigated. Timolol activates the enzyme activities of HCA I and HCA II. In HCA I and II, the enzyme kinetic results clearly showed that timolol increases the value of *V*max but does not influence the value of *K*m. The enzyme kinetic method showed that timolol noncompetitively activates HCA I and II activities through the formation of a ternary complex consisting of the enzyme, the substrate, and timolol. These results indicate that timolol binds apart from the narrow cavity of the active site.

AutoDocking results showed that timolol binds at the entrance of the active site cavity in a region where the proton shuttle residue, His 64, of HCA I or II, is placed. The enzyme kinetic and AutoDocking results showed that timolol might weakly bind near the proton shuttle residue, His 64, to accelerate the proton transfer rate from His 64 to the buffer components. It is known that efficient activators of carbonic anhydrase possess a bulky aromatic/heterocyclic moiety and a primary/secondary amino group in their molecular structure. Timolol has a heterocyclic moiety and a secondary amino group, which are typical structures in efficient activators of carbonic anhydrase.

抄録　β‐ブロッカーであるチモロールは緑内障の治療薬として用いられる。チモロールは炭酸脱水酵素阻害剤である緑内障治療薬と併用して用いられるので、炭酸脱水酵素の活性に対してチモロールがどの様な影響を与えるかを検討した。チモロールは炭酸脱水酵素の酵素活性を非拮抗的に活性化することが判った。その原因を知るために、AutoDock により、チモロールの結合部位を推定した。それによるとチモロールは炭酸

脱水酵素の His64 の付近に結合し、炭酸脱水酵素の律速段階である水素イオンの移動を活性化することにより、炭酸脱水酵素の活性を活性化することが判った。

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