Structure of Prostaglandin D Synthase Complexed with Drug Molecules

Medicines can help people suppress the feelings of headaches or period pains. But at the same time, there are side effects. Sometimes people feel sleepy when they use medicine. Medicine containing aspirin or indometasine inhibits cyclooxygenese (COX) that catalyzes the reaction from arachidonic acid to prostaglandin (PG) H_2 in the arachidonic acid cascade (Fig. 1). PGH_2 is the starting compound which is utilized to obtain other types of prostaglandin, PGD_2, $PGF_{2\alpha}$ and PGE_2, and so on. Each PG has a specific function in the tissue concerned. PGD_2 in the brain has the function of promoting sleep, however, in other tissues, PGD_2 is produced from mast cells as an allergic mediator or inflammatory mediator. $PGF_{2\alpha}$ was the first compound to be discovered which has the role of contracting the oviductal smooth muscle. PGE_2 has the role of regulating body temperature and also promotes wakening. The inhibition of the production of PGH_2 by medicine causes side effects due to the lack of specific prostanoids in various tissues. Each prostaglandin is formed by a specific enzyme, PGD synthase, PGF synthase and PGE synthase, respectively. As for the design of anti-allergic drugs, the structure of human hematopoietic PGD synthase (H-PGDS) is the most potent target, as demonstrated in an allergic asthma model with prostaglandin D receptor gene-disrupted mice [1], and as also demonstrated by transgenic mice that overproduce PGD_2, thus exacerbating asthmatic reactions [2].

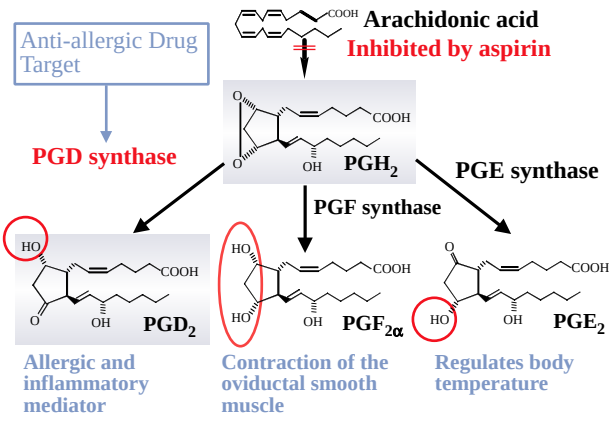

Fig. 1. Biosynthetic Pathway of Prostaglandins (PGs) with compositional formulas and their roles. The difference of each PG is the stereochemistry of hydroxyl group or functional group.

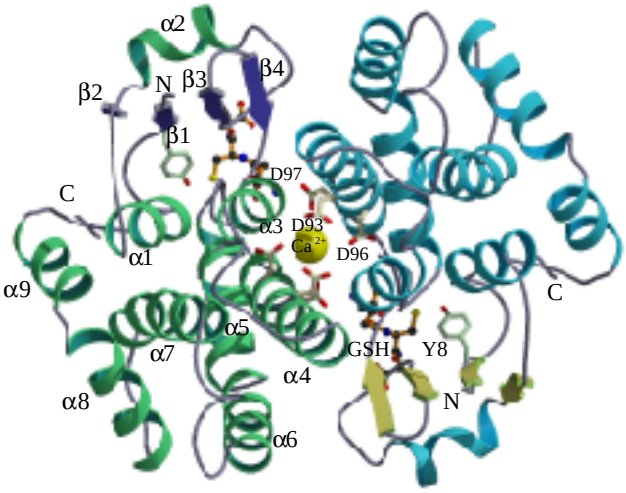

Fig. 2. The whole structure and the metal binding site of human H-PGDS. The metal binding site was found at the dimer interface where six aspartates exist.

H-PGDS absolutely requires glutathione (GSH) for stereospecific isomerzation from PGH_2 to PGD_2. We determined the X-ray structures of the native and substrate analog complexes of human H-PGDS with glutathione (GSH) in the presence of Ca^{2+} or Mg^{2+}. The metal binding site was found at the dimer interface where six aspartates, Arg14 and GSH construct a large hydrogen bond network regulated by metal ions (Fig. 2). Ca^{2+} reduces the K_m value for substrate, while, Mg^{2+} reduces the K_m value for GSH as well as the substrate. Mg^{2+} shows a remarkable change in the hydrogen bond

network, promoting a free rotation of Arg14, which results in a low K_m value for GSH. The Ca^{2+}- and Mg^{2+}-bound complex structures with two kinds of substrate analogs provide snapshots of successive binding of the substrate analogs to the enzyme, indicating a possible novel reaction mechanism, regulated by the metal ion, for the isomerization from the 9,11-endperoxide group of PGH_2 to PGD_2 with the 9-hydroxy-11-keto group.

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References

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[3] T. Inoue, N. Okazaki, H. Shishitani, S. Kinugasa, Y. Okano, H. Matsumura, Y. Kai, M. Yamamoto, T. Kumasaka, D. Irikura, N. Uodome, O. Hayaishi, and Y. Urade, in preparations.

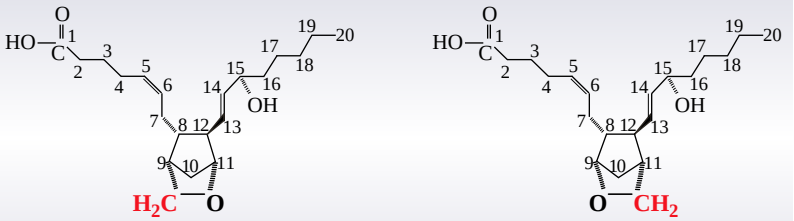

Fig. 3. Two kinds of substrate analogs used for the complex structure analysis. The difference is in only the location of the oxygen atom in the cyclopentane ring.

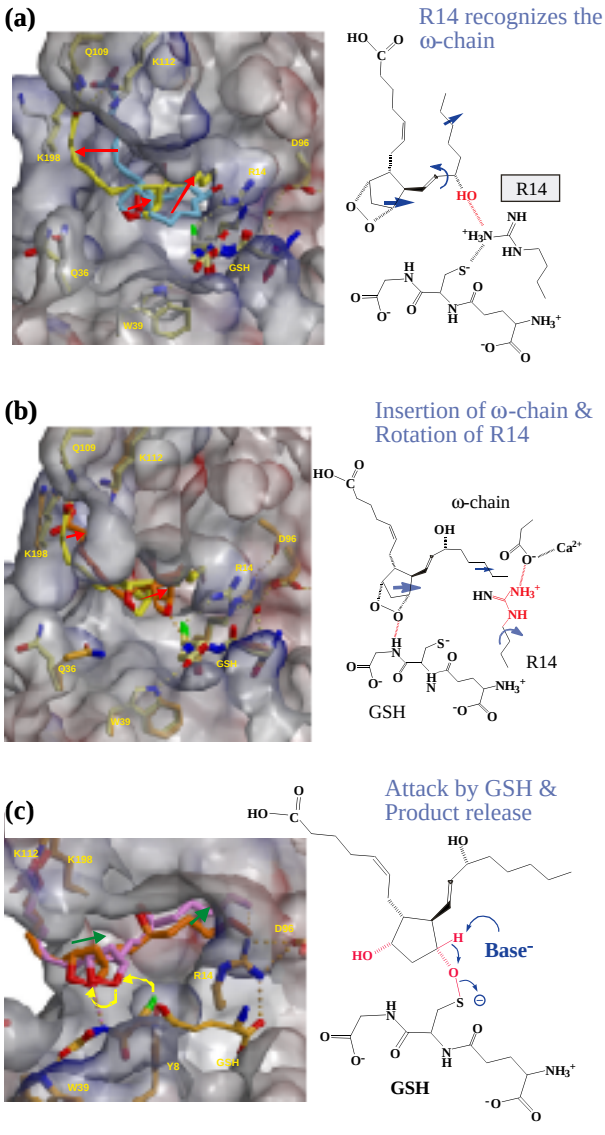

Fig. 4. We obtained three different binding motifs of the substrate analogs in the presence of Ca^{2+} or Mg^{2+}, providing X-ray snapshots of the successive binding of the substrate analogs to the enzyme. We are now proposing the novel reaction mechanism on the right side of each figure.