15-keto-prostaglandin E_2, the metabolite of prostaglandin E_2, may work as biased agonist for EP2 and EP4 receptors.

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Prostaglandin E_2 (PGE_2) are known to be involved in inflammation and cancer. There are four subtypes of E-type prostanoid (EP) receptors, EP1 to EP4, for PGE_2. Among them, EP2 receptor and EP4 receptor are frequently confused because they are both coupled with Gs-protein. Although, we have previously shown that EP4 receptor is additionally coupled with Gi-protein. PGE_2 is metabolized to 15-keto-PGE_2 by the action of 15-hydroxy prostaglandin dehydrogenase. 15-keto-PGE_2 has been considered as an inactive form of PGE_2. However, we thought 15-keto-PGE_2 may activate EP receptor subtypes as biased agonist, since the only difference between PGE_2 and 15-keto-PGE_2 is a hydroxyl or a carbonyl functional group at position 15. Here we found that 15-keto-PGE_2 acts as a full agonist for EP2 receptor, while acting as a partial agonist for EP4 receptor. In addition, when compared to the affinity and efficacy, it was found that PGE_2 is tend to activate EP4 receptor, but when it is metabolized to 15-keto-PGE_2, it prefers to activate EP2 receptor. Thus, 15-keto-PGE_2 may not be just an inactive form of PGE_2, but may involve in the biological and physiological roles that need to be elucidated.