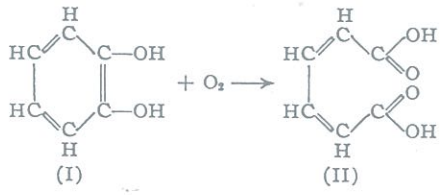
第15回 早石 修レクチャー

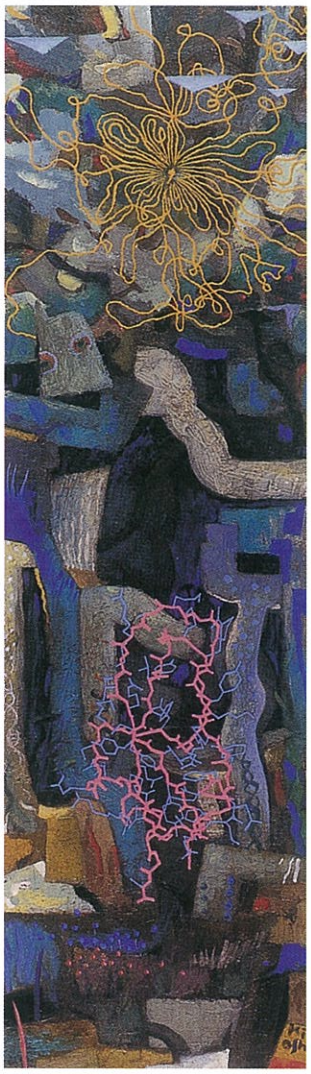
The 15th Osamu Hayaishi Lecture

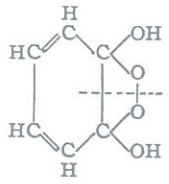
Pyrocatechase[1,2] of *Pseudomonas* sp. catalyzes the oxidative cleavage of the aromatic ring of catechol (I) to *cis–cis*-muconic acid (II). Subsequent work has shown that pyrocatechase requires ferrous ion[3] and sulfhydryl containing compounds[4] for maximum activity, although the mechanism of electron transport as well as the nature of intermediate steps has remained unknown.

We wish to report some experimental results using O_2^{18} and H_2O^{18} which may aid in elucidating the mechanism of this unique enzymatic reaction. When the reaction was conducted in the presence of H_2O^{18}, O^{18} was not detected in the product, *cis–cis*-muconic acid. In the presence of O_2^{18}, however, essentially all the oxygen enzymatically introduced into *cis–cis*-muconic acid was shown to be derived from molecular oxygen (Table I). The results clearly demonstrate that pyrocatechase is an oxygen transferase rather than a dehydrogenase and no hydration reaction is involved in the over-all process. *cis–cis*-Muconic acid semialdehyde is therefore excluded as an intermediate since any known mechanism of enzymatic aldehyde oxidation involves hydration. A compound such as (III) appears to be a more likely intermediate in the pyrocatechase reaction. Orthobenzoquinone ap-



(I) (II)





(III)

The structural basis of G protein coupled receptor signaling

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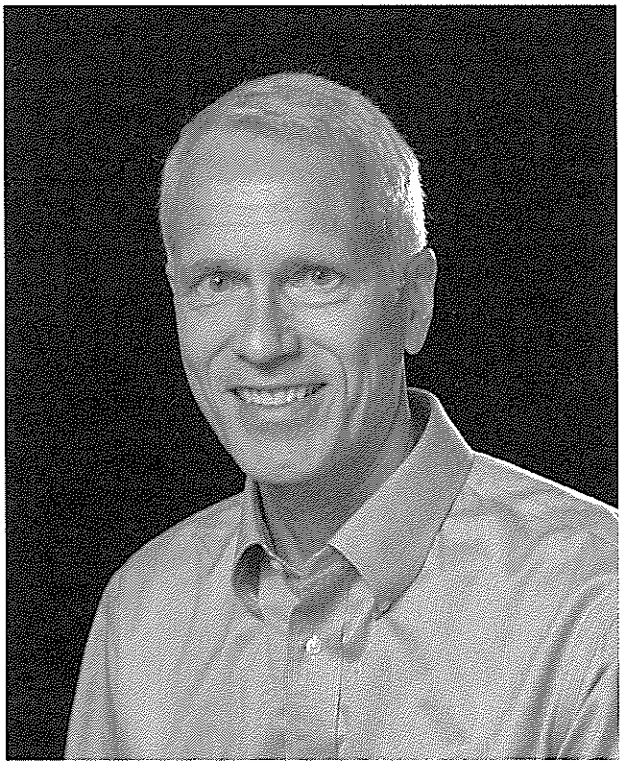
主催

早石レクチュア実行委員会



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略歴

1977年ミネソタ大学の生物学および化学の学位を取得。1981年イエール大学医学部を卒業し、1984年ワシントン大学Barnes病院の内科研修を修了。1984年から1989年までデューク大学のロバート・レフコーヴィッツ博士の研究室で研究員として勤務。その後、1990年にスタンフォード大学医学部に移動し、2000年より同大学教授。

2012年ノーベル化学賞　受賞

The structural basis of G protein coupled receptor signaling

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GPCRs conduct the majority of transmembrane responses to hormones and neurotransmitters, and mediate the senses of sight, smell and taste. The beta 2 adrenoceptor is a prototypical Family A GPCR that mediates physiologic responses to adrenaline and noradrenaline. We have obtained three-dimensional structures of the beta 2 adrenoceptor in inactive and active conformations, as well as a structure of this receptor in complex with the G protein Gs. We have also used fluorescence, EPR and NMR spectroscopy to study the dynamic properties of the receptor, and to map ligand-specific conformational changes. I will discuss what these studies have taught us about the structural basis of GPCR function.

G蛋白質共役受容体シグナル伝達の構造基盤

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GPCRは、ホルモンや神経伝達物質などに反応して様々なシグナルを伝えるだけでなく、視覚、嗅覚、味覚の伝達にも重要な分子である。β_2アドレナリン受容体は、アドレナリンとノルアドレナリンに対する生理反応を媒介する典型的なFamily A GPCRである。我々は、不活性型及び活性型のβ_2アドレナリン受容体の立体構造に加え、G蛋白質Gsと複合体を形成した受容体の立体構造を解明することに成功した。さらに、蛍光、EPR、NMRを利用し、受容体の動力学的解析及びリガンド特異的な受容体の構造変化を調べた。講演では、構造を基盤としたGPCRのシグナル伝達機序について議論したい。

The similarity of pyrocatechase to other enzymes which catalyze oxidative rupture of aromatic rings of certain phenolic compounds was recently reviewed by Crandall.[5] In addition to pyrocatechase, homogentisicase,[6] 3-hydroxyanthranilic acid oxidase[7,8] and protocatechuic acid oxidase[4] appear to belong to this new class of metallo-protein enzymes which introduce two oxygen atoms directly across the aromatic bond adjacent to the phenolic group with simultaneous rupture of the aromatic structure.

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