S06-5 Chemical and biological studies on cannabinoid biosynthesis

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Cannabis sativa is well known to produce structurally-unique secondary metabolites called cannabinoids, and in my laboratory, various types of studies on cannabinoids have been conducted since more than 40 years. In this symposium, I present novel evidences which have recently been obtained by these investigations.

When I investigated the biosynthetic pathway of tetrahydrocannabinolic acid (THCA), the principle of *C. sativa*, I discovered that THCA is biosynthesized through oxidocyclization of cannabigerolic acid, and identified a biosynthetic enzyme (THCA synthase) catalyzing this reaction. After purification of THCA synthase, a gene encoding this enzyme was cloned. Analysis of the amino acid sequence showed that THCA synthase is a flavoprotein similar to berberine bridge enzyme which mediates formation of a berberine skeleton. Furthermore, I have recently determined the crystal structure of THCA synthase, and have now attempted to analyze the reaction mechanism of THCA synthase based on its structure.

I also have investigated the reason why *C. sativa* produces cannabinoids. Consequently, I confirmed that THCA acts as a necrosis-inducing factor in *C.sativa* and that THCA treatment causes serious damage to *Cannabis* mitochondria. Based on these results, I concluded that THCA is biosynthesized as important factor that participates in physiologically important events in *C. sativa*.