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INVOLVEMENT OF CARBOXYLESTERASE IN THE HYDROLYSIS OF ESTER DERIVATIVES OF VARIOUS STEROID COMPOUNDS

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ABSTRACT

Carboxylesterase, a member of serine esterases, is responsible for the activation of ester and amide prodrugs, and is found in various tissue. Mammalian CES comprise a multigene family, and their isozymes are classified into five fundamental groups (CES1-CES5) based on the homology of the amino acid sequence. The human CES1 isozyme, hCES1, and CES2 isozyme, hCES2, play a major role in the bioconversion of prodrugs and exhibit 48% homology. Their substrate specificity are quite different. hCE1 can hydrolyze a wide variety of substrates, especially substrates modified by small alcohol group. Most prodrugs such as oseltamivir, temocapril are hydrolyzed by hCE1. In contrast, hCES2 mainly hydrolyzes prodrugs into which alchol group of pharmacological active drug is modified with a small acyl group. Interestingly, hCE1 is able to catalyze transesterification, but not hCE2. Their distinct substrate specificity is explained by the size and structure of active center. However, there is no information about their hydrolyzing capacity for ester derivatives of steroid compounds. In this study, we examined hydrolysis of various ester prodrugs with steroidal structure, in order to confirm the substrate recognition by hCE1 and hCE2.

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