EXPRESSION AND DISTRIBUTION OF TISSUE CARBOXYLESTERASES THAT CATALYZE DRUG ESTER METABOLISM

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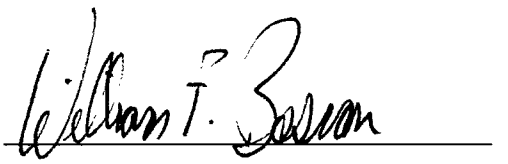

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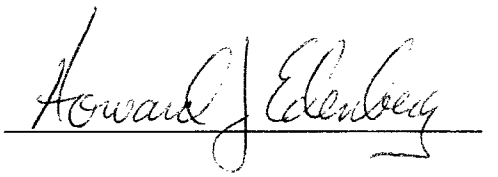

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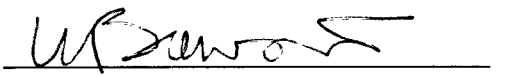

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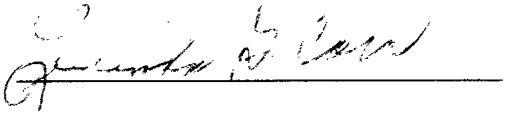

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ABSTRACT

Carboxylesterases play an important role in drug and environmental ester metabolism. A human liver carboxylesterase (hCE-1) catalyzes the hydrolysis of a variety of drug esters and the ethyl transesterification of cocaine to form cocaethylene. The goals of my research were to determine the tissue distribution of cocaine carboxylesterases in rat, rabbit and human, to identify new members of the human carboxylesterase family, and to characterize the role of tissue carboxylesterases in cocaine and opioid ester metabolism.

In rat tissues, HPLC analysis of reaction products showed that liver had the highest capacity for both cocaine hydrolysis and transesterification, suggesting that liver is the primary site for the enzymatic hydrolysis of cocaine methyl ester. Western blot analysis demonstrated that the expression of rat hydrolase A, a homolog of hCE-1, was prominent in rat liver and lung. Male rat livers also had significantly greater capacity than females in the hydrolysis of cocaine.

A new human carboxylesterase, hCE-2, was cloned and sequenced. Amino acid sequence alignments among mammalian carboxylesterases suggest that humans express different esterase isoforms than do rats, hence the esterase metabolism may be different in rats and humans. It appears that rabbit carboxylesterases are more homologous to the human forms.

The capacity of rabbits to metabolize cocaine was evaluated from the tissue content of the esterase homologous to hCE-1 and the kinetic constants of the purified enzyme. Liver had the highest capacity for cocaine hydrolysis. In the

rabbit, the form homologous to hCE-1 is highly expressed in liver and lung while the form homologous to hCE-2 was highly expressed in liver and the gastrointestinal tissues. hCE-1 catalyzed the hydrolysis of synthetic opioid meperidine to meperidinic acid. This enzyme may be important in the pharmacokinetics of opioid ester elimination.

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