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cDNA CLONING OF THREE NEW FORMS OF RAT BRAIN CYTOCHROME P450 BELONGING TO THE CYP4F SUBFAMILY*

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Summary: Three cDNA clones, designated 4f-8, 4f-34 and 4f-41, coding for three new forms of cytochrome P450 belonging to the CYP4F subfamily were isolated from an untreated rat brain cDNA library. cDNA 4f-8, 4f-34 and 4f-41 coded for proteins of 522, 526 and 537 amino acids, respectively, and their amino acid sequence similarity to CYP4F1 ranged from 71 to 80%. These new P450s were thus named CYP4F4, 4F5 and 4F6, respectively. Northern blot analysis revealed that the expression levels of these forms of P450 in the brain were somewhat low and that similar forms of subfamily 4F P450 were expressed in liver and kidney at a relatively high level compared with brain. No CYP4A expression was detected by Northern blot analysis in untreated rat brain mRNA. All three clones were *in vitro*-translatable using a reticulocyte lysate system. These results show that multiple forms of subfamily 4F P450 exist in the brain and that the subfamily 4F P450 may be one of the major forms of P450 in the brain.

Many members of the hepatic cytochrome P450 family exist in reasonably large quantities and most of them participate in catalyzing the metabolism of xenobiotics and carcinogens. In extra-hepatic organs, on the other hand, it seems that some specific forms of P450 present in smaller quantities may play important physiological roles.

In the kidney, for instance, P450 isoenzymes belonging to CYP4A subfamily, of which the primary catalytic activity is the ω–hydroxylation of fatty acids including prostaglandins (PG) and arachidonic acid, appear to be the major forms present (1-4). Schwartzman *et al.* reported that the major renal cytochrome P450 ω-hydroxylation product of arachidonic acid metabolism, 20-hydroxyeicosatetraenoic acid (20-HETE), modulates renal transport activities (5) and its further metabolites via renal cyclooxygenase, 20-hydroxy-PGG_2 and 20-hydroxy-PGH_2, possess vasoconstrictor properties (6).

In the brain, in spite of its generally low cytochrome P450 specific content, there is an accumulating body of evidence for the existence of multiple forms of cytochrome P450 (7-11) and for the functionality of its monooxygenase system (12-14). Recently, Sequeira and Strobel (15) demonstrated brain microsomal catalytic activity toward imipramine and differences in the efficacy

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