ABSTRACT

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Title of diploma thesis: In vitro biotransformation study of fenofibric acid

Fenofibric acid is a hypolipidemic agent that acts through PPARα and contributes to treatment of many types of dyslipidemias. It is the active metabolite of fenofibrate, but can be also administrated by itself. Concerning its metabolism, the majority of fenofibric acid is conjugated with glucuronic acid, while a minor amount yields a reduced metabolite. Reduced fenofibric acid is also an active substance. The identity of the enzymes participating in the reducing metabolic process has not been revealed yet. The current study investigated this carbonyl reduction in human liver subcellular fractions and by the use of nine recombinant cytosolic carbonyl-reducing enzymes of the AKR and SDR superfamilies. Enzymatic activity toward fenofibric acid reduction appeared in both cytosol and microsomes and was found that affinity of cytosol is greater while velocity in microsomes is higher. Of the nine tested enzymes, five reductases were identified to play role in the reduction of fenofibric acid. The highest activity was exhibited by CBR1, followed by AKR1C3, AKR1C2, AKR1C1 and AKR1B1. Our finding of significant contribution of microsomal fraction to the carbonyl reduction of fenofibric acid stimulates further investigation on microsomal reducing enzymes.