ESTERASES INVOLVED IN HYDROLYSIS OF NAFAMOSTAT MESILATE IN HUMAN LIVER CYTOSOL
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Nafamostat mesilate (NM) is a potent inhibitor of a variety of serine proteases including trypsin, thrombin and C1 esterase. This drug is widely used for the treatment of acute pancreatitis and disseminated intravascular coagulation. Previously, we reported that carboxylesterases were mainly responsible for NM hydrolysis in human liver microsomes (18th annual meeting of JSSX, 2003). In the present study, we examined characteristics of esterases involved in the NM hydrolysis in human liver cytosol. Kinetic analysis indicated that $V_{\text{max}}$ and $K_m$ values were 9.82 ± 0.33 nmol/min/mg protein and 197 ± 22 µM, respectively. The $V_{\text{max}}/K_m$ value for human liver cytosol was 49.8 ± 5.8 µL/min/mg protein and approximately 3 times higher than that for the corresponding liver microsomes (15.0 ± 4.4 µL/min/mg protein). The hydrolytic activity for NM in human liver cytosol was inhibited to lesser extents (0-20%) by typical esterase inhibitors (1-25 µM); phenylmethylsulfonylfluoride (an inhibitor for various serine hydrolases), diisopropylfluorophosphate and bis-p-nitrophenylphosphate (inhibitors for carboxylesterase and cholinesterase). In contrast, arachidonyl trifluoromethyl ketone (1-10 µM), inhibitors for phospholipase A2 and fatty-acid amide hydrolase, suppressed the cytosolic activity in a concentration-dependent manner. These results suggest that esterases responsible for the NM hydrolysis in human liver cytosol and microsomes may be different from each other.