P5 EFFECT OF (N-HYDROXYMETHYL)-2-PROPYLPENTAMIDE ON RAT HEPATIC CYTOCHROME P450

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ABSTRACT

The effect of (N-hydroxymethyl)-2-propylpentamide (HPP), a novel valproic acid (VPA) derivative possessing anticonvulsant activity[1], on rat hepatic cytochrome P450 was studied in *ex vivo* and *in vitro* system. In *ex vivo* study, HPP at a dosage of 100 and 200 mg/kg/day and VPA 250 mg/kg/day were given intraperitoneally to male Wistar rats once daily for 7 days. On the day after, rat liver microsomes were prepared and determined for total CYP contents and CYP activities (ethoxyresorufin *O*-dealkylase for CYP1A1, methoxyresorufin *O*-dealkylase for CYP1A2, benzyloxy- & pentoxyresorufin *O*-dealkylase for CYP2B1&2B2 and aniline 4-hydroxylase for CYP2E1). In *in vitro* study, inhibitory effects of HPP at final concentrations of 0.1, 1, 10, 100 and 1000 μM on β–napthoflavone-induced CYP1A1&1A2, phenobarbital-induced CYP2B1&2B2 and ethanol-induced CYP2E1 activities were studied. The results showed that VPA at the dose studied did not have any effect on total CYP contents and CYP activities. Whereas HPP 100 and 200 mg/kg/day significantly induced CYP1A1 and CYP2B1&2B2 activities. In addition, HPP at 100 and 1000 μM significantly inhibited CYP2B1&2B2 activities *in vitro* with IC_{50} about 1000 μM. These results suggested that the inhibitory effect of HPP on CYP2B1&2B2 activities may be in part responsible for the increasing effect on barbiturate sleeping time after single dose administration[1]. The induction effect of HPP, but not VPA, on CYP1A1 and CYP2B1&2B2 activities after administration for 7 days may result from direct effect of HPP or its metabolites. Further studies are needed to clarify the metabolic pathways of HPP and the CYP involved as well as the effect of HPP on human CYP. *In vivo* studies to verify the potential of drug interaction and carcinogenic risk are also needed.

Reference

1. Pataranich C, Tantisira MH, Tantisira B. Pharmacological evaluation of anticonvulsant activity of (N-hydroxymethyl)-2-propylpentamide. Final report to the Faculty of Pharmaceutical Sciences, Chulalongkorn University. 1998.