Chapter IV

Conclusion

Investigation of anticonvulsant activity of VPA and VPP has been studied and carried out both *in vitro* and *in vivo.* Experimental design employed MES and PTZ seizure. Anticonvulsant activity of various doses of VPA , expressed as percentage protection, has tested at different pretreated time. It was found that the peak protection effect of VPA against the MES was at 30 minutes whilst that of VPP was at 15 minutes and the pretreated times observed were further used as an optimal pretreated time for the experiment on PTZ seizure. The ability to protect the animal from the MES and PTZ seizure were then evaluated. The calculated ED_{50} from the MES was 221.72 mg/kg for VPA and 81.19 mg/kg for VPP. The results indicated considerably clear that VPP had greater potency in protection against MES than VPA and furthermore it had shorter onset. In PTZ seizure experiments, the calculated ED_{50} was found to be 108.84 mg/kg for VPA and 77.89 mg/kg for VPP. These results demonstrated that as a broadspectrum anticonvulsant VPP was superior to VPA in both potency and onset time.

In vitro studies on degradation of VPP have been performed by incubating the test compound with either liver or brain homogenate from 0 to 240 mintues. , There was a remarkably and significantly increase in VPA concentration in liver homogenate specimens. This indicates the hepatic degradation of VPP to VPA. In parallel with an analysis for VPA, GABA analysis has been performed and it was found that GABA concentration in both liver and brain homogenates, after VPP being added, was slightly different but not significantly from control level.

Based on the results obtained, it is suggestive that in the liver, VPP might be degraded into VPA and comparatively stable 2-pyrrolidinone (see pathway 1 in Figure 8) rather than into an unstable intermediate compound leading to the

formation of equimolar amount of VPA and GABA (see pathway 2 in Figure 8). However, this proposed hypothesis should be investigated further *in vivo*.

The effect of VPP on cortical GABA levels was carried out in male rat brain by using microdialysis method. The results obtained did not demonstrate significant and remarkable difference in cerebral cortical GABA concentration between VPA treated and VPP treated rats group. Therefore it could be postulated that VPP was unlikely to be degraded to GABA. These *in vivo* results conformed with the result obtained from previous *in vitro* study that VPP did not increase GABA levels in brain homogenate.

As previously mentioned , it appears that VPP *per se* posseses a stronger potency than VPA as a broad spectrum anticonvulsant with a short onset of action. Its mechanism of anticonvulsant activity is unlikely to be associate with the degradation of VPP into VPA and GABA as previously postulated by Wicharn Janwitayanuchit (1992). More studies are needed to elucidate the mechanism of action to VPP as an anticonvulsant.