CHAPTER V

DISCUSSION

Piperine is the compound that possesses pharmacological effects on several biological systems such as the central nervous system, cardiovascular system, and respiratory system. Among all known effects, the remarkable actions on central nervous system belong to its depressant and anticonvulsant properties at considerable doses, though the exact mechanisms of action are still unknown. In the study of Pei (1983), it was found that the compound 7903, which is the derivative of piperine, decreased monoamine levels in the brain of experimental animals. In experimental animals, the cardiovascular effects of piperine had been shown to be the decrease in heart rate and blood pressure which were suspected to be the result of its intervention with sympathetic nervous system (P. Dhumma-upakorn, unpublished observation). It was found recently that piperine may produce an extent of drug interaction by diminishing hepatic drug metabolism. This notion was suggested by the finding that piperine behaved as a non-specific inhibitor of hepatic drug metabolizing enzymes in rats. However, Shin and Woo (1985) revealed that piperine administration in the pharmacological doses had no significant effect on microsomal mixed-function oxidase system in the liver. Up to this point, it is conceivable that piperine displays a wide variety of pharmacological actions

some of which may be considered as potential candidates for therapeutic purposes.

In this study, the attempt had been made to specify the effect of piperine on the liver and brain mitochondrial monoamine oxidase system which is the major metabolic pathway for both endogenous and exogenous monoamine substances. The foundational basis for such a prospective was dued to the reported anticonvulsant and toxic effects of piperine on the central nervous system in animals. The speculation was posed on the possible link between monoamine oxidase activities and aboved mentioned effects of piperine and, moreover, the potential implication of piperine in, at least, pharmacological research. The results thus far indicated that both type A and type B of liver mitochondrial MAO activities in vitro were markedly inhibited by piperine at considerably low concentrations in a more or less complex manner. This inhibitory profile was not, nevertheless, demonstratable in brain mitochondrial preparations. The possible explanation for this incompatible finding, on one hand, may be the discrepancy in enzymatic behaviours between the liver and brain mitochondrial MAO system. On the other hand, the in vitro assay conditions for brain mitochondrial MAO activity which were adopted from those used in the liver mitochondrial preparations and/or the preparative technique may be inadequate for supporting central MAO activity. It had been shown that MAOs from peripheral and central sources possess different properties in some aspects, e.g., the membrane lipid environment, compositional ratio of type A and type B, cofactor(s) needed. In

this study, brain mitochondrial preparations reveal inconsistent MAO activity towards most amine substrates tested and did not responded to piperine application. The only substrate which can reveal a fair extent of central MAO activity in the present assay protocol is dopamine, all the others reveal inconsistent and very low enzymatic activity. In the case of dopamine, the increased oxygen consumption rate caused by the addition of substrate was totally abolished by preexposure to pargyline, an MAOI, but was unaffected by the application of piperine in a comparable concentration with that used in liver preparations. The application of piperine in high concentrations was not tenable because of technical problems. Piperine is very sparingly soluble in water thus it has to be dissolved in absolute ethanol. The ethanol concentrations in assay mixtures increased in parallel with those of piperine and then markedly affected enzymatic activity. In addition, piperine tended to precipitate as very fine particles in the assay mixtures if applied in very high concentrations.

Considering experimental results, it is possible to predict that certain observable effects of piperine may be, at least in part, derived from its inhibitory action on MAO system. The important role of mitochondrial MAOs in controling levels of cellular amines needs no emphasis. In this connection, the profound CNS stimulating effects observed in animals receiving high doses of piperine could probably be the result of central MAO inhibition which consequently led to accumulation of monoamine neurotransmitters in the brain. This postulation is

based on the assumption that responses of brain MAOs to piperine are similar to those of liver MAOs. It had been shown by several groups of investigators that the administration of monoamine oxidase inhibitors (MAOIs) to experimental animals gave rise to remarkable CNS stimulation. Those treated animals displayed increased locomotor activity, hyperresponsiveness to external stimuli, tremor, hyperventilation and even convulsion.

At the present time, the exact role of central monoamine neurotransmitters in experimental convulsion had not been convincingly illustrated. It is conceivable that enhancement of synaptic transmission at specific brain area(s) may, by certain mechanisms, be essential to alleviation of global neuronal bursting activity during convulsive episode. If this happens to be the case, the appropriate doses of piperine may provoke selective stimulating effect to certain brain area(s) with "high responsiveness or low threshold" to piperine action thereby rendering apparent anticonvulsant property. It is unlikely, however, to make much elaboration on this matter as long as the effect of piperine on brain MAOs has not been convincingly illustrated.

CHAPTER IV

CONCLUSION

In this study, the assay of MAO activity was developed by measuring oxygen consumption rate as the indicator of enzymatic activity. This assay method was used to investigate the effect of piperine on enzymatic activity of MAO toward various monoamine substrates and the results obtained suggest the followings:

1. Piperine possesses remarked inhibitory action to both types (MAO-A and MAO-B) of rat liver mitochondrial MAO activity.

2. The inhibition profile was complicate and may not be competitive in nature.

3. The preliminary result from the study on rat brain mitochondrial preparations was not satisfactory and conclusive interpretation based solely on such data cannot be made.

4. Overall, the experimental results suggest the possible relationship between MAO inhibition and CNS stimulatory effect of piperine.