# CHAPTER VII
# CONCLUSION

Ample evidences indicate that altered control of craniovascular nociceptive system is an important step in migraine pathogenesis. Recently, it has been shown that migraine patients are supersensitive to infusion of nitric oxide (NO) donating agent. Based on this finding, the hypothesis of "NO supersensitivity" as a cause of migraine headache has been proposed. However, the exact mechanism of such supersensitivity is still a question. Serotonin (5-HT) has been accepted to play a pivotal role in migraine pathogenesis. Changes in this neurotransmitter level were demonstrated to correlate with the attack of migraine. The present study was conducted to investigate relationship between hyposerotonin and cranial microvascular responses to NO as well as its effect on activation of craniovascular nociceptive system. The results showed that infusion of NTG produced dose-dependent pial arteriolar dilatation. This vasodilator effect was significantly increased in PCPA-treated groups. Electron microscopic study revealed that exposure to NO donor produced considerable changes in cerebral microvessels, characterizing by increased microvillous formation, increased endothelial pinocytosis, swelling of endothelial mitochondria, focal swelling of endothelial cells and swelling of perivascular astrocytic footplate causing partial separation of microvessels from adjacent brain tissue. These anatomical changes were significantly more prominent in hyposerotonin group. Exposure to NO donor (NTG 10 mg/kg) also activates Fos immunoreactivity in various brain areas, mostly related to nociceptive information processing. Fos immunoreactivity can be demonstrated in trigeminal nucleus caudalis, lateral reticular nucleus, nucleus tractus solitarius, inferior olive,

paraventricular nucleus of hypothalamus and habenular. However, the numbers of Fos positive neurons in control and hyposerotonin groups were not different.

The data above indicate that meningeal and cerebral microvessels undergo functional and ultrastructural changes after exposure to NO. These changes can be enhanced by prior depletion of 5-HT. The enhanced microvascular response and ultrastructural changes response to NO in 5-HT depleted animals in this study supported that hyposerotonin may be a possible mechanism underlying NO supersensitivity. The proposed mechanisms are shown in Figure 4.1. This observed also implied the role of hyposerotonin in modulation of cranial vascular response to NO in migraine patients.

**Trigeminovascular Action of Serotonin**

| Normal | Serotonin Depletion |
|---|---|
| 1. Cerebral vessel constriction | 1. Ineffective control of cerebral vessel constriction |
| 2. Inhibition of vasoactive peptides release | 2. Ineffective control of vasoactive peptides release |
| 3. Presynaptic inhibition of TNC | 3. Ineffective presynaptic inhibition of TNC |
| 4. Inhibition of postsynaptic potential of TNC | 4. Ineffective inhibition of postsynaptic potential of TNC |

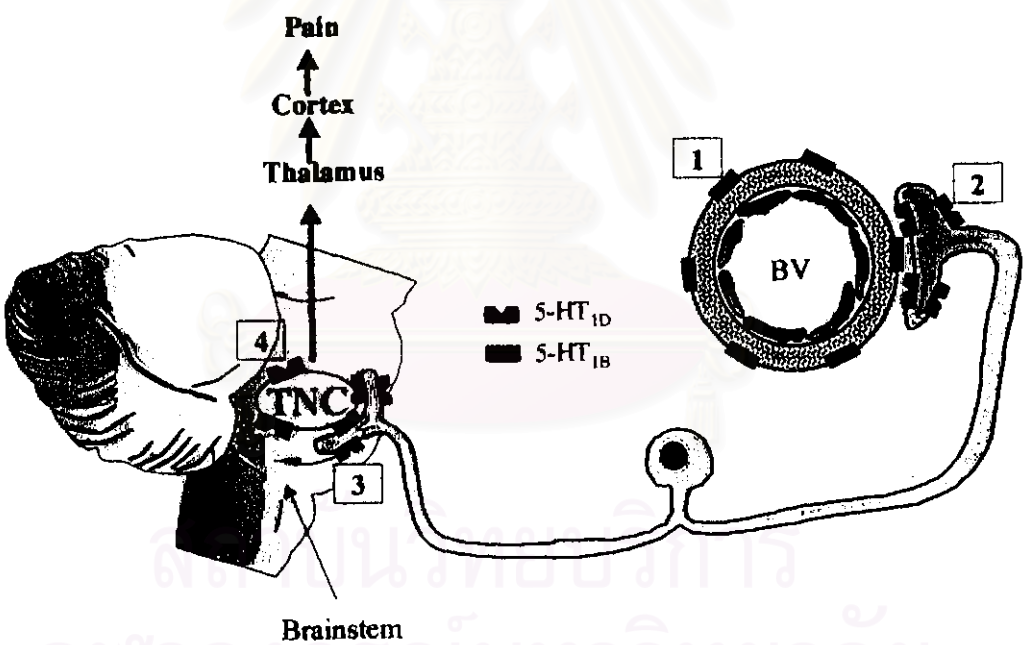


**Figure 7.1.** The proposed mechanism of hyposerotonergic state-induced NO supersensitivity (BV=Cerebral blood vessel, 5-HT=Serotonin, TNC=Trigeminal nucleus caudalis)