# CHAPTER III
# SIGNIFICANCE OF PROBLEM AND OBJECTIVE

The pathophysiological basis of migraine is still controversy. The development of this disease may be attributed to both neuronal and vascular mechanisms. During migraine attacks, the intracranial extracerebral blood vessels supplying tissues such as the dura mater (e.g. middle meningeal artery and it dural branches, pial arteries) are thought to dilate and thereby activate surrounding perivascular sensory nociceptive fibers (Lance, 1993; Friberg, 1996). The dilatation may then trigger a sterile localized neurogenic inflammation mediated by vasoactive neuropeptides such as SP, neurokinin A and CGRP released from activated perivascular sensory nerve fibers (Moskowitz, 1993). Levels of CGRP were increased in cranial venous blood during a migraine attack (Goadsby et al., 1990). Elevated CGRP levels in external jugular venous blood during a migraine attack are normalized concurrently with headache relief by subcutaneous injection of sumatriptan, a 5-$HT_{1B/1D}$ receptor selective agonist (Gallai et al., 1995).

The smooth muscle cells of the intracranial blood vessels and the peripheral and central terminals of the trigeminal nerve sensory fibers express receptors of the 5-$HT_{1B}$ and 5-$HT_{1D}$ subtypes, respectively. (Hartig et al., 1996; Longmore et al., 1997). Activation of 5-$HT_{1B}$ receptors causes selective vasoconstriction of certain extra- and/or intracranial blood vessels (Daholf and Hargreaves, 1998). Activation of 5-$HT_{1D}$ receptors causes prejunctional inhibition of proinflammatory neuropeptide release from sensory nerve terminals in the meninges

(Rebeck et al., 1994) and inhibition of neurotransmitter released within the trigeminal nucleus caudalis (Goadsby and Hoskin, 1996).

Previous research indicates that migraine attacks may be related to unstable serotonergic neurotransmitter. Migraine sufferers have chronically low plasma 5-HT levels (Curran et al., 1965) but these have been shown to double to control level during migraine attacks (Ferrari and Saxena, 1993). It is now thought that there is an increased turnover of 5-HT in plasma during interictal periods which results in low levels between attacks. These are associated with an increase in the main breakdown product of 5-HT, 5HIAA, in urine of migraine patients (Sicuteri et al., 1961).

NO is thought to be involved in migraine at several levels. In the vascular endothelium, its appears to act as a large endocrine gland with a potent vasodilatory role. In the periphery, NO is thought to be a pain mediator. In its central role, NO is produced by neurons and glial cells and operates the process of neurogenic inflammation, it participates in plasma protein extravasation at the levels of sensitive trigeminal fibers (Moskowitz, 1991).

Experimental human headache models design by intravenous infusion of NTG offer unique possibilities in the study of NO mechanisms in migraine. These experiments demonstrated that migraine patients more often experience a migraine-like headache in association with NTG administration than do non-migraineurs (Olesen et al., 1993). Thus, migraineurs are hypersensitive to NTG-induced headache and most likely therefore to NO. An increased headache response could, however, reflect a greater general sensitivity to pain, or it could be due to increased physiological sensitivity to NO. Moreover, the increased sensitivity to

the NO donor was reflected not only increased headache in migraineurs but also increased dilatation of the cerebral arteries. Indeed migraineurs were found to be more sensitive in this aspect as well (Thomsen et al., 1994). The supersensitivity to NO and the low plasma 5-HT levels have been proposed to explain abnormal vasomotor responses in migraine patients. However, the association between both of them cannot be regarded as proven.

As previously mentioned, the key findings are; first, the dilatation of cranial vessels can activate perivascular sensory nerve fibers that innervated by trigeminal nerve and then activate the neural pathway concerning pain processing. Second, migraine attack is associated with a chronically drop in plasma 5-HT levels and an increased excretion of 5-HIAA in urine following an attack. Third, 5-$HT_{1B/1D}$ receptors are demonstrated in trigeminovascular afferents and intracranial blood vessels. The selective receptor agonists of this receptor subtype are used for treatment migraine attacks. And finally, migraine patients exhibit a greater sensitivity to NO than do control subjects.

Based on these findings, we performed the following animal experimental model for investigating the association between NO supersensitivity and the 5-HT depletion on (1) the response of vasomotor (2) the activation of neural pain processing pathway and (3) the ultrastructural changes of cerebral microvessels. The cerebrovascular response was studied using intravital pial microvascular monitoring, the neural activity in pain pathway was evaluated by Fos immunoreactivity and the ultrastructural changes was performed by electron microscopic study.

## OBJECTIVE OF THIS STUDY

The aim of this study are:-

1. To study the effects of NO on vasomotor responses in normal and 5-HT depletion rats.

2. To compare the vasomotor responses to NO between normal and 5-HT depletion rats.

3. To study the effects of NO on ultrastructural changes of cerebral microvessels of normal and 5-HT depletion rats.

4. To compare the effects of NO on ultrastructural changes of cerebral microvessels obtained from normal and 5-HT depletion rats.

5. To study the effects of NO on modulation of nociceptive system in neural pain pathway of normal and 5-HT depletion rats.