CHAPTER I
INTRODUCTION

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Migraine is an important and fascinating disorder. Its importance is due to the high prevalence and disabling severity. The total sum of suffering caused by migraine is probably higher than that with any other kinds of headache. Migraine headache afflicts ~ 10-20 per cent of the population. There are two main types of migraine. The first, migraine without aura (previously called common migraine), is characterized by headache attacks lasting 4-72 hours. The headache is usually severe, unilateral pulsating, and accompanied by nausea, vomiting, photophobia and phonophobia. In the second type, migraine with aura (previously called classic migraine) the attacks are preceded by neurological symptoms called aura (visual, sensory, speech or motor distortions). Otherwise, the headache is similar to that in migraine without aura. The exact pathogenesis of migraine is unknown. Neuronal and vascular theories of migraine have evolved in the past few decades indicating that migraine is probably a vascular disorder which has its triggering of origin in the brainstem, and that the connections and regulation between neurons and vessels are at the heart of migraine. It seems that neuronal and vascular theories are complementary and not in any way exclusive.

Several theories exist which attempt to explain the pathogenesis of migraine. Based on the theory of Wolff (1963) migraine was considered to be a vasospastic disorder with a vasoconstriction during the migraine aura and a vasodilatation during the headache phase. Several studies measuring regional cerebral blood flow have shown that attacks of

migraine with aura are initiated by a focal reduction in regional cerebral blood flow, which occurs most commonly in the posterior part of the brain (Lauritzen and Olesen, 1984). Subsequently, the low-flow region spreads forward to contiguous areas. Lauritzen (1994) proposed that these observed flow changes were secondary to the electrical phenomenon of spreading depression first described by Leao (1944). Cortical spreading depression is a short-lasting depolarization wave that moves across the cortex at a rate of 3-5 mm/min. It must be noted, however, that this phenomenon has never been recorded in human during a migraine attack.

In the past, mechanisms of migraine and other spontaneous headaches are difficult to evaluate. Patients cannot reach the investigators in the early phases of attack which pathophysiologically are the most interesting, and true pathogenic mechanisms are difficult to distinguish from consequences of the attack. But now, the understanding of migraine is rapidly increasing and coherent models of its mechanisms are now available. Several compounds have been proposed as headache-inducing agents such as reserpine, histamine, nitroglycerin (NTG), sodium nitroprusside and so on. Among these agents, only nitroglycerin model has been validated.

Iversen and his coworkers (1989a) developed the intravenous NTG as an experimental model of vascular headache. They focused on NTG-induced headache because the mechanism of action of NTG is presumably purely vascular and it has been at least partly elucidated. Some characteristics of NTG-induced headache are already known (Ekbom, 1968; Sicuteri et al., 1987) and NTG challenge has even been suggested as a diagnostic test to discriminate migraine from other headaches (Peter, 1953). Moreover, NTG-induced headache is an

annoying side effect when treating patients with angina pectoris and a work hazard in the ammunition industry. According to Iversen et al. (1989a), the effect of the NTG-induced headache was reproducible. The quality was moderately severe, usually throbbing, and bifrontal in location. It reached maximum within 2.5-5.5 minutes (medians) at various doses and declined rapidly after NTG discontinuation. The reproducibility of headache intensity and character was satisfactory in the retest experiment.

Recently, the effects of NTG on cerebrovascular responses and headache in normal volunteers have been extensively characterized (Dahl et al., 1990). NTG induces dilatation of cerebral arteries and extracranial arteries as well as extremity arteries but does not change cerebral blood flow, indicating that it acts predominantly on the arteries (Dahl et al., 1990). In normal volunteers, intravenous infusion of NTG results in a steady-state headache after approximately 10 minutes. The headache is maintained at a relatively constant level for up to several hours if the infusion continues (Iversen et al.,1989a). After discontinuation of the infusion, headache rapidly disappears, as expected from the very short half-life of NTG in plasma. It has been shown that N-acetylcysteine, a donor of SH-groups, augments both arterial responses and headache intensity when used as a pretreatment before NTG infusion (Iversen, 1992a). Dose-response relationship between NTG and headache have been delineated, and a ceiling effect has been documented around the dose of 0.5 μg/kg/min (Iversen et al., 1989b). A similar ceiling effect pertains to arterial dilatation. The percentage dilatation of the superficial temporal artery is significantly higher than that of the radial artery. Moreover, augmentation effect of N-acetylcysteine on the response of the superficial temporal is higher than that of the radial artery. Though NTG

affects blood vessels throughout the body, there is thus evidence of increased sensitivity and differing modulatory mechanisms in the cranial as compared to systemic arteries. This illuminates the fact that NTG and therefore nitric oxide (NO) causes headache, but no pain in the rest of the body. Sicuteri et al., (1987) reported that migraine patients are more sensitive to NTG than non-migraineurs. In addition, Iversen et al., (1989a) found that migraine patients more often experience migraine-like headache during NTG administration than controls. Recent evidence indicated that migraine patients are supersensitive to NTG induced headache (Olesen et al., 1993). Olesen et al., (1993) found that headache in migraineurs was significant more intense than in normal subjects. After NTG infusion stopping, headache rapidly diminished or disappeared in non-migraineurs, whereas minimal improvement developed in migraine patients. None of the control subjects but 14 out of 17 migraineurs required specific migraine treatment after the infusion. Within 24 hours after NTG infusion, 11 of 17 migraineurs developed a headache that they characterized as a typical migraine. Thomsen et al., (1993a) and Zanette, (1991) also demonstrated that migraineurs exhibit a greater sensitivity to NTG than do control patients. Their data also suggested that the middle cerebral artery of migraineurs underwent greater vasodilatation when a NO donor is administered than in control patients. Wei and colleagues (1992) showed that local application of NTG to the pial surface induces calcitonin gene-related peptide (CGRP) release from perivascular nerve fibers. This implies that the observed increase in CGRP during migraine attack may be secondary to NO formation.

Possibly, nitric oxide synthase (NOS), an enzyme responsible for the production of NO, is upregulated in migraineurs and provides increased

sensitivity to NO. Furthermore, the NTG-induced headache in migraineurs more often fulfilled the operational diagnostic criteria for migraine without aura and after the infusion, most of the migraineurs developed a migraine attack (Olesen et al., 1993). It is not yet understood why migraine sufferers respond with more intense headache to NO donor than healthy controls. An increased headache response could reflect a greater general sensitivity to pain or it could be due to increased physiologic sensitivity to NO. These data support that NO supersensitivity may be an important molecular mechanism of migraine pain (Thomsen et al., 1993a; Sandler, 1995).

Activation of the trigeminovascular system is likely to be responsible for the head pain of migraine. C-fibers of the trigeminal nerve innervate dural and pial blood vessels throughout the cavarium (Arbab et al., 1986). Their cell bodies lie in the trigeminal ganglion and project to the trigeminal nucleus caudalis and dorsal horn of C_1 and C_2 spinal cord levels. These connect with second-order neurons that project to the thalamus. From there, information is disseminated to higher cortical centers. Tracing studies have confirmed that fibers innervating cerebral vessels arise from the trigeminal ganglion contain substance P (SP) and CGRP. Moreover, the cell bodies in the trigeminal ganglion are bipolar neurons that innervate the large cerebral arteries and dura mater and arise from the first or opthalmic division of the trigeminal nerves. Stimulation of these cranial vessels, such as the superior sagittal sinus, is certainly painful in humans (Feindel et al., 1960). Electrical stimulation of trigeminal ganglion results in the release of the vasoactive peptides, CGRP and SP (Goadsby et al., 1988; Buzzi et al., 1991). These peptides dilate blood vessels and, in addition, SP promotes protein leakage from blood vessels. Thus, these events lead to a sterile inflammation within the

dural vasculature (Moskowitz, 1993a). By using Fos immunocyto-chemistry, a method for looking at activated cells, after meningeal irritation with blood or chemical stimulation, Fos expression is reported in the trigeminal nucleus caudalis (Nozaki et al., 1992). Stimulation of the superior sagittal sinus, Fos-like immunoreactivity is seen in the trigeminal nucleus caudalis and in the dorsal horn at the C_1 and C_2 level in cat and rat (Kaube et al., 1993; Strassman et al., 1994). Based on initial molecular biological studies, the trigeminal ganglion and presynaptic nerve terminals may preferentially contain 5-HT_{1D} receptor subtype (Rebeck et al., 1994) whereas the blood vessels expressed 5-HT_{1B} receptor subtype (Hamel et al., 1993; Branchek et al., 1996). In addition to the physiologic responses seen with trigeminal ganglion stimulation, there are structural changes seen in the blood vessels of the rat dura mater. These include mast cell degranulation and platelet aggregation in postcapillary venules (Dimitriadou et al., 1991 and 1992). Platelet and mast cells are mainly serotonin storage organell. Such changes may be related to the changes in serotonin (5-HT) level, another neurotransmitter that has a role in migraine pathogenesis (Curran et al., 1965; Artico et al., 1998).

Recently, research has also focused on role of 5-HT in pathogenesis of migraine. There has been extensive investigation that points to role of various 5-HT receptor subtypes. At present, classification of 5-HT receptors has been based on operational and structural data into 14 different receptor subtypes (Martin, 1994). Many lines of evidence show that the 5-HT_1-like receptor plays a major role in the pathophysiology of migraine. This receptor subtype is found in a much higher concentration in the wall of intracranial arteries than in the extracranial arteries. By this reason, intravenous injection of a selective 5-HT_1-like receptor agonist,

sumatriptan, was introduced and found to abort acute attack of migraine headache within 15-30 minutes (Humphrey et al., 1988). Iversen et al. (1993) studied the effect of sumatriptan in treating migraine attacks on NTG-induced headache as well as its effect on the large artery responses. They found that sumatriptan (6 mg subcutaneously (sc)) decreased the NTG-induced headache. Moreover, the temporal and radial artery diameters decreased after sumatriptan administration compared to placebo (Iversen and Olesen, 1996). These findings correspond to obviously finding that the middle cerebral artery dilatation detected during migraine attack can be constricted back to normal caliber by sumatriptan (Friberg et al., 1991). It is thought that 5-HT receptor agonists function in migraine by modulating the activity of the trigeminovascular system, thereby inhibiting the transmission of pain impulses into the brainstem from the trigeminal nerve to higher parts of the brain.

Recently, Fozard (1995) suggested that the involvement of 5-HT and NO in the initiation of migraine by the endogenous 5-HT-containing neurons, activate 5-HT_{2B}/5-HT_{2C} receptors on endothelial cells of the cerebral vasculature to release NO (Fozard and Kalkman, 1994; Schmuch et al., 1996). NO would, by directly activating sensory neurons, induce neurotransmitter release, plasma extravasation, pain and hyperalgesia. The result would be induction of the "*sterile inflammatory response*" that believed to be the key step in the development of migraine pain. The concept of this hypothesis rests primarily on two facts: first, that an experimental drug tool, m-chlorophenylpiperazine (mCPP), 5-HT_{2C} receptor agonist, triggers migraine in selected subjects at doses which yield peak plasma concentrations (Brewerton et al., 1992; Panconesi and Sicuteri, 1987); second, that a number of compounds whose only common pharmacological property to high (nanomolar) affinity for 5-

HT_{2C} receptors protect against migraine when given prophylactically (Fozard & Kalkman, 1994; Schmuch et al., 1996).

Several lines of evidence suggested that 5-HT might play an important role in migraine pathogenesis (Pradalier and Launay, 1982; D'Andrea et al., 1982). The postulated involvement of 5-HT in migraine was first substantiated by an observation that migraine attacks in some patients were associated with an increase in the main breakdown product of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA) in urine after migraine attack (Sicuteri et al., 1961). In addition, the mean 5-HT content in platelets was lower during headache (Curran et al., 1965). Thus, the study of 5-HT and its receptor subtypes are a key to understand the molecular mechanisms of migraine pathogenesis. Recently, it has been shown that 5-HT_1 receptor can be divided into several subtypes: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C} and 5-HT_{1D} receptors, which all have nanomolar affinity for 5-HT and 5-HT_2, 5-HT_3 and 5-HT_4 which have micromolar affinity for 5-HT (Martin and Humphrey, 1994). Recent studies have suggested that the different 5-HT receptor subtype may play different roles in pain regulation; even opposite effects have been described. For example, a number of studies indicated that activation of 5-HT_1 receptors reduce nociceptive responsiveness (Eide et al., 1988, 1990 and 1991). On the contrary, activation of 5-HT_2 receptors may increase the transmission of nociception in the spinal cord. This effect may be due to the stimulation of SP release from perivascular afferents (Eide and Hole, 1991). Recent observation also showed that the 5-HT systems may show long-lasting plasticity which resulting in an up- or down-regulation of 5-HT receptors. Administration of a drug or other types of stimuli may induce functional changes lasting for a long time after the stimulation has ended. Experimental data indicated that lesioning or reduced activity of the 5-HT

neuronal system may be associated with sensitivity to 5-HT (Eide & Hole, 1993). In migraine, the changes in receptor sensitivity and their clinical correlates have been studied. Down-regulation of 5-HT_2 receptors has been previously reported in headache free period (Govitrapong et al., 1992). Moreover, the up-regulation of 5-HT_2 receptors was reported in the transformed migraine patients (Srikiatkhachorn et al., 1994). The correlation between a decrease amount of central 5-HT_2 receptor and disappearance of migraine headache could be observed in the elderly (Fontes et al., 1990).

As previously mentioned, the key findings are; first, migraine attack is associated with an unstable serotonergic neurotransmission. Second, migraine patients exhibit a greater sensitivity to NO than do control patients. Third, 5-HT_{2C} trigger NO release when activated. Finally, the role of 5-HT receptor subtypes and plasticity in the 5-HT systems may be modulation of headache pain. Based on this findings, we design the following experiment to investigate the association of NO supersensitivity and the plasticity in 5-HT systems in animal model.