CHAPTER I

INTRODUCTION

Migraine is a common episodic headache disorder that affects 18% of female, 6% of male and 4% in children [1] and ranks around the world's most disabling medical illness. Migraine headache is characterized by attacks comprising various combinations of headache and gastrointestinal symptoms such as nausea, vomiting, etc. The severity of headache ranges from moderate to severe. An epidemiological study has documented its high prevalence socio-economic and has a negative effect on the quality of life. According to the international Headache Society (2005) migraine can be divided into two major subtypes. The first, migraine without aura, is a clinical syndrome characterized by headache and associated symptoms such as nausea, vomiting and photophobia. In the second type, migraine with aura (previously known as classical migraine), is characterized by the focal neurological disturbance. The migraine aura may be defined as any neurological disturbance that appears shortly before or during the development of migraine headache. The creeping fashion commonly distinguished between migraine aura and epilepsy. Several investigators have described their own migraine aura. Lashley's scintillation-scotoma developed symmetrically in the visual fields, suggesting a cortical localization of the symptoms [22]. The disturbance started at the visual field centre and propagated to the peripheral (temporal) parts within 10-15 min, while function returned to normal within another 10-15 min. The aura symptoms indicated a wave of intense excitation in the primary visual cortex.

In 1944, Leao reported his observation concerning a specific pattern of the electroencephalogram (EEG), which could be triggered by non-noxious stimulation. This electrophysiologic phenomenon is characterized by an increase followed by a decrease of EEG activity in focal cortical areas, especially occipital lobe. The excitation-depression wave gradually expands forward and normally disappears at the central sulcus. Based on the similarity in time course and pattern of spreading, Leao proposed that an electrophysiologic phenomenon, which was later termed cortical spreading depression (CSD), might be the mechanism underlying the aura phase of migraine [21]. Though CSD correlates well with the clinical feature of neurological

deficits, occurring during the aura phase, the relationship between this phenomenon and the generation of headache is still inadequately explained.

The pathogenesis of migraine is not clearly understood. The recent concept emphasizes the role of trigeminal nociceptive system in the development of migraine. In this hypothesis, migraine headache is driven by the activation and sensitization of peripheral neurons in the trigeminal ganglia that innervated the cranial vessel and meninges, also the activation of central trigeminovascular neurons which are located in the trigeminal nucleus caudalis (TNC) of the brainstem (C_1 and C_2 regions of spinal cord). The trigeminal system works as a final common pathway of headache development. It plays a pivotal role in mediating the information regarding the cranial nociception to higher brain centers including thalamus and somatosensory cortex. The function of trigeminal system is strong influence of both coming activities from peripheral nociceptors as well as the descending control higher centers. Moreover, its hyperexcitability is an essential step in pathogenesis of various primary headache including migriaine and cluster headache. Actually, the control of trigeminal system is extremely complicated and involves several chemical messengers, both small molecule transmitters and peptides.

Nociceptin/orphanin FQ (N/OFQ) is a 17-amino acid neuropeptide with close similarity to the opioid peptides (Meunier, 1995). N/OFQ has selective affinity for the orphan opioid receptor-like (ORL-l) G-protein coupled receptor (GPCR). N/OFQ has been the subject of a large and growing number of studies intended to understand its physiological role in the nervous system. ORL-1 receptor is abundant expression widely in the central nervous system including the cerebral cortex, limbic system, brainstem and several areas involved in pain perception. Although, most of the studies have focused on the roles of N/OFQ in pain modulation, the effects of it remain controversial, N/OFQ produces hyperalgesia (increasing pain) or analgesia (reducing pain) (Yamamoto et al., 1999). Moreover, the precise role of N/OFQ in the involvement of the trigeminal nociceptive system, and the linkage between cellular action of N/OFQ and its behavioral effect are still unclear.

Distribution study suggests pathophysiological involvement of N/OFQ in the mechanism of cortical excitability and neurogenic headaches. It has been demonstrated that plasma N/OFQ level correlates with the frequency of migraine attacks. However, the mechanism that N/OFQ triggers migraine attack is not well understood. The present study was designed to investigate the effect of N/OFQ on the trigeminal nociceptive system by determined the respond of cortical activity evoked by CSD. We also studied the expression of c-Fos protein in TNC and TRPV1 in trigeminal ganglia as indicators of trigeminal nociception.