CHAPTER I

INTRODUCTION

Migraine is a very common neurobiological headache disorder that is caused by increased excitability of the central nervous system. The pathophysiology of migraine is not fully understood. However, migraine pain is associated with dural inflammation. This inflammation sensitizes peripheral neurons in the trigeminal ganglion and central trigeminovascular neurons, resulting in throbbing pain and cutaneous allodynia, respectively.

Glutamate, the excitatory neurotransmitter, has been reported to involve in the activation and sensitization of the trigeminovascular nociceptive system [1]. Among several subtypes of glutamate receptors, the *N*-methyl-D-aspartate receptors (NMDA receptors) have been implicated in the activity-dependent plastic changes that lead to the generation and maintenance of central sensitization and, thus, pain hypersensitivity. The major mechanism that potentiates NMDA channel activity is phosphorylation of the receptors. NMDA receptors are phosphorylated at different sites by a variety of kinases. Experiments in animals show that NMDA receptors are phosphorylated by protein kinase C (PKC) at serine-896 of NMDA receptor NR1 subunit after peripheral inflammation or peripheral noxious stimulation. This phosphorylation occurs in the endoplasmic reticulum and initiates the trafficking of NMDA receptor to the synapse, ultimately enhancing glutamate current [2, 3]. This may suggest a role for NMDA receptor phosphorylation in central sensitization.

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that has a role in endogenous pain modulatory system. The attack of migraine has been observed to be associated with low level of serotonin. It has been assumed that the descending inhibitory serotonergic pathway involved in the control of pain is defective in migraine sufferer, and that 5-HT depletion increases this defect and induces migraine attacks [4, 5]. Alteration of this pain-controlled system has been demonstrated in chronic daily headache (CDH) patients associated with analgesic overuse. Chronic analgesic exposure induces a low 5-HT state that leads to up-regulation of pro-nociceptive 5-HT_{2A} receptors. Activation of the 5-HT_{2A} receptors elevates intracellular calcium, and

activates various kinases. Thus, this plasticity may potentiate central sensitization [6]. Although, the mechanism underlying the relationship between low level of serotonin and migraine attack is still unclear, change in NMDA receptor expression and NMDA receptor phosphorylation of central neurons in trigeminal pathway may be another possible explanation.

The objectives of this study are to investigate:

1. The effect of dural stimulation on NMDA receptor expression, NMDA receptor phosphorylation, and trigeminal nociception in normal condition.
2. The effect of serotonin depletion on NMDA receptor expression, NMDA receptor phosphorylation, and trigeminal nociception induced by dural inflammation.
3. The relationship between the phosphorylation of NMDA receptor and trigeminal nociception in normal and serotonin-depleted rats.

The knowledge from this study may provide better understanding about the role of serotonin and the phosphorylation of NMDA receptor in the trigeminal nociception.