

## CHAPTER I

### INTRODUCTION

#### 1.1 Statement of the problems and objectives

VGSCs are transmembrane ion channels responsible for influx and efflux of sodium ions. The fluctuation of sodium ions causes the electrogenesis of membrane potential that, in case of spontaneous action, can lead to pain. Until now, at least nine structurally related  $\alpha$ -subunit isoforms of VGSCs have been identified: Nav<sub>v</sub>1.1, Nav<sub>v</sub>1.2, Nav<sub>v</sub>1.3, Nav<sub>v</sub>1.4, Nav<sub>v</sub>1.5, Nav<sub>v</sub>1.6, Nav<sub>v</sub>1.7, Nav<sub>v</sub>1.8, and Nav<sub>v</sub>1.9 (Amir et al., 2006). Each isoform has different distribution, electrophysiological properties, and pharmacological properties (Krafte and Bannon, 2008; Wood et al., 2004). VGSCs can be distinguished by susceptibility to tetrodotoxin (TTX), which is a toxin isolated from puffer fish, into TTX-sensitive (TTX-S) and TTX-resistant (TTX-R) subfamilies (Amir et al., 2006). The altered activity of VGSCs has strongly been found in peripheral neurons associated with either inflammatory or neuropathic pain (Joshi et al., 2006; Kim et al., 2001; Nassar et al., 2004; Siqueira et al., 2009; Strickland et al., 2008; Thakor et al., 2009) and has been suggested to contribute to the activation of pain pathways and the development of increased pain status (Amir et al., 2006; Cummins et al., 2007; Devor, 2006).

Dental pain is a culprit of waste and impairment in quality of life. The cause of dental pain is injuries to dental pulp, which is a tissue richly innervated with nociceptive fibers (Hildebrand et al., 1995). Studies of VGSCs in dental pulp have

revealed that at least four VGSC isoforms are expressed in dental pulp, including Nav1.6, Nav1.7, Nav1.8, and Nav1.9 (Beneng et al., 2010; Henry et al., 2005; Henry et al., 2009; Luo et al., 2008; Padilla et al., 2007; Renton et al., 2005; Warren et al., 2008; Wells et al., 2007). Nav1.8 and Nav1.9 are both TTX-R VGSCs. They are dominantly found in nociceptive nerve fibers (Akopian et al., 1996; Coward et al., 2000; Henry et al., 2009; Padilla et al., 2007) and are involved in inflammatory pain (Cummins et al., 2007; Krafte and Bannon, 2008). In human permanent teeth with painful pulpitis, increased expression of Nav1.8 and Nav1.9 has been found (Renton et al., 2005; Warren et al., 2008; Wells et al., 2007). Therefore, the up-regulation of Nav1.8 and Nav1.9 in dental pulp following inflammation may be the cause of anesthetic failure in teeth with inflamed dental pulp. The current research focus is on a new generation of selective sodium channel blockers for the treatment of inflammatory pain. Thus, Nav1.8 and Nav1.9 might be the targets for the development of novel treatments and novel anesthetic agents used in teeth with painful pulpitis.

A lower density of sensory innervation in primary teeth than in permanent teeth has been observed (Johnsen and Johns, 1978; Rodd and Boissonade, 2001; 2002) and this may be the reason behind the notification that primary teeth have less pain sensitivity than permanent teeth. However, the expression of Nav1.8 and Nav1.9, which are located in neuronal membranes, in primary teeth with and without inflammation and the relationship between the expression of sodium channels, particularly Nav1.8 and Nav1.9, and pain status in human primary teeth has never been reported.

Therefore, in this study, we hypothesized that the expression of Nav1.8 and Nav1.9 in pulpal tissues increases in painful human primary teeth and correlates with the pain intensity. The subjects participating in this study were requested to evaluate pain score before tooth extraction. The quantity of the proteins PGP9.5, MMP-9, Nav1.8, and Nav1.9 in dental pulp was determined using western blot analysis. The aims of this study were as follows.

**Aim 1:** To investigate whether pulpal inflammation leads to increased levels of Nav1.8 and Nav1.9 expression in the dental pulp of human primary teeth

**Aim 2:** To investigate whether the levels of Nav1.8 and Nav1.9 expression are correlated with the severity of pulpal pain in dental pulp of human primary teeth

## 1.2 Anticipated benefits

The anticipated benefit of this study was to prove whether the levels of Nav1.8 and Nav1.9 expression are increased in painful pulpitis and are correlated with pain intensity. If the expression of Nav1.8 and Nav1.9 are increased and associated with pain intensity, Nav1.8 and Nav1.9 may be the targets in the development of novel drugs for the treatment of pulpal inflammatory pain and novel anesthetics for the treatment of painful pulpitis in children.