CHAPTER I
INTRODUCTION

1. Background and Rationale

Paclitaxel (Taxol®), isolated from the bark of the Pacific yew tree (*Taxus brevifolia*), is an important drug widely used in cancer chemotherapy (Rowinsky, 1997). Since its initial isolation in 1966 and subsequent structural determination in 1971, a tremendous number of researches focusing on the molecular mechanisms and efficacy of paclitaxel have been performed (Kumar, 1981; Jordan et al., 1993; Henningsson et al., 2001; Ferlini et al., 2003 Needleman et al., 2005). Paclitaxel has been approved by the Food and Drug Administration (FDA) for the treatment of advanced ovarian cancer in December 1992 and for metastatic breast cancer in April 1994 and remains in use in clinical practice since then.

Paclitaxel is the first among a new class of chemotherapeutic agents, generally known as microtubule-stabilizing anticancer agents (Shiff et al., 1979; Ringel and Horwitz, 1991). These drugs bind to β-subunit of tubulin heterodimer, the key constituent protein of microtubules. The binding of these drugs accelerates the polymerization of tubulin, and stabilizes the microtubules, thereby inhibiting their depolymerization. This inhibition of microtubule depolymerization results in the arrest of the cell division cycle between the prophase and anaphase stages, eventually leading to apoptosis of the cells. Since, cancer cells posses higher activity of division and proliferation, they are more susceptible to this group of drugs.

Although paclitaxel has been used as a potential anticancer agent, it can generate several complications such as hypersensitivity reactions (Weiss et al., 1990), hematologic toxicity (Rowinsky et al., 1993), and peripheral neuropathy. Paclitaxel-induced neuropathy is characterized by predominant

sensory impairment such as numbness and paresthesia in the extremities (Rowinsky et al., 1993). In an animal model of paclitaxel-related neuropathy, histopathological examination showed axonal degeneration in the nerve (Cavaletti et al., 1995; Authier et al., 2000; Chentanez et al., 2003; Persohn et al., 2005), collapse and fragmentation of myelin sheet (Persohn et al., 2005), and increased density of microtubules (Cavaletti et al., 1995; Authier et al., 2000).

Although neuropathy caused by paclitaxel has been studied by many investigators, the molecular mechanisms underlying this phenomenon are still unclear. MAPKs (Mitogen-activated protein kinases) are a family of protein kinases comprised of extracellular signal-regulated kinase (ERK), c-Jun NH_2-terminal kinase (JNK) and p38 kinase and are implicated in the proliferation, differentiation and survival of various cell types. Paclitaxel-induced activation of MAPKs, which plays an important role in nerve cell viability, has been reported. For example, in cortical neurons, JNK activation is required for paclitaxel-induced apoptosis (Figueroa-Masot et al., 2001). Besides, a sustained activation of ERK induces both tau phosphorylation and apoptosis during paclitaxel treatment in human neuroblastoma cell lines (Guise et al., 2001). In PC 12 cells, transfected JNK3 significantly enhanced cell death after paclitaxel treatment (Waetzig and Herdegen, 2003). In another type of sensory neuropathy, diabetic neuropathy, activation of MAPKs has been linked to the pathogenesis. Activation of ERK and p38 in primary sensory neurons has been associated with cell death in response to high glucose condition and p38 inbition results in the improvement of neuropathy in diabetic rats (Purves et al., 2001; Price et al., 2004).

From the above evidence, it is possible that paclitaxel might induce peripheral neuropathy via activation of MAPKs. However, the phosphorylation status which indicates the activity of MAPKs in the peripheral nervous system (PNS) has not been studied in this condition. Thus, the objective of this work is

to study the state of MAPK phosphorylation in the PNS of paclitaxel-treated rats. The result will be essential for finding the new potential treatment for paclitaxel-induced neuropathy.

2. Research Question

Is there any alteration in the phosphorylation of MAPKs in primary sensory neurons and associated glial cells in paclitaxel-treated rats?

3. Objective of the Study

To study MAPK activity in primary sensory neurons and associated glial cells in paclitaxel-treated rats compared with the controls

4. Hypothesis

MAPK phosphorylation is altered in primary sensory neurons and associated glial cells in paclitaxel-treated rats relative to the controls

5. Key Words

Paclitaxel Taxol MAPKs Peripheral neuropathy

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6. Expected Benefits and Applications

1. To verify an alteration in the phosphorylation of MAPK in the PNS of paclitaxel-treated rats. If MAPK phosphorylation is altered, this may suggest the role of MAPKs in paclitaxel-induced neuropathy

2. If the activation of MAPKs by paclitaxel is observed, MAPK inhibitors will be used to try to alleviate the neuropathy. Furthermore, if the treatment is successful in animals, the data will form the basis for further clinical trials.

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