

CHAPTER 1

INTRODUCTION

Narcotic drugs have become a serious health and social problem that obstructs socio-economic development as well as threat to national security. The current national strategy on the reduction of drugs supply and demand for drugs has proven effective for drug control. However, the success of efforts does not depend on those measures alone. The cooperation among the global community is a key element in ensuring a drug-free society. Many countries and international organizations have come to work together to find the best solution to tackle these drug menaces.

During the 20th century, there have been recurrent episodes of cocaine abuse in the United States that have achieved epidemic proportions. Although the total number of people using the drug has decreased in the past decade, cocaine-related biomedical and psychosocial problems remain a major public health problem in the United States and many other countries in the world (reviewed by Mendelson & Mello, 1996). Cocaine use rose to epidemic levels in the early and mid-1980s, after which it declined in prevalence. However, between 1994 and 1998, the number of new cocaine users per year increased 82 percent, from 514,000 to 934,000. Several factors account for this recent increase in cocaine use, including the ease of its administration, the increased availability and purity of the drug, reduced cost, and the misperception that the recreational use of cocaine is safe (Lange & Hillis, 2001). The deaths of several celebrities in many years later, association with the non-therapeutic use of cocaine, have focused

widespread attention on the problem of cocaine abuse. In 1999, an estimated 25 million Americans admitted that they had used cocaine at least once; 3.7 million had used it within the previous year; and 1.5 million were current users. During the same year, cocaine was mentioned in 30 percent of all drug-related visits to emergency departments. Cocaine is the most commonly used illicit drug among subjects seeking care in hospital emergency departments or drug-treatment centers. In addition, it is the most frequent cause of drug-related deaths reported by medical examiners (Lange & Hillis, 2001).

Cocaine has been shown to be associated with myocardial ischemia and MI independently of the administration route, the amount ingested and the frequency of use (Kloner & Rezkalla, 2003). Most patients with cocaine-related acute MI are young and male and have a low coronary risk factor profile for atherosclerosis and have previously normal epicardial coronary arteries (Lange & Hillis, 2001). The pathogenesis of cocaine-related MI has been reported to be multifactorial including increased myocardial oxygen demand, marked vasoconstriction of the coronary arteries, enhanced platelet aggregation and thrombus formation and accelerated atherosclerosis (Erwin, et al., 2004). Cocaine-related acute MI due to acute coronary thrombosis in patients with low coronary risk profile and normal epicardial coronary arteries have been reported (Meltser, et al., 2004). Acute MI due to intense coronary spasm and subsequent intra-coronary thrombosis in patients with normal epicardial coronary arteries have also been reported in other clinical situations (Comerci, et al., 2005). These findings suggest that, in humans, certain individuals are at a greater risk for severe cocaine-induced cardiovascular complications and finally, cause of sudden death. Therefore, studies examining toxicity that identify individuals at high or low risk for cocaine-induced cardiovascular complications would be clinically relevant.

A number of hypotheses have been proposed to explain the occurrence of cardiac complications including, central sympathetic or autonomic hyperresponsiveness, direct cardiac effects possibly related to inhibition of sodium channel activity, alter cocaine metabolism, or a direct toxic action on the coronary in vasculature and/or the heart. Experimental studies have not clearly established the involvement of the sympathetic nervous system in mediating cardiovascular response to cocaine. Although several investigators have presented evidence for a role of the sympathetic nervous system using ganglionic blockade, direct sympathetic recordings have revealed a sustained sympathoinhibitory effect (reviewed by Branch & Knuepfer, 1994). There are classically mentioned to the mode of action of cocaine enhancing supersensitivity of adrenergic innervated organs in response to norepinephrine and other catecholamines. Firstly, cocaine blocks the uptake process of norepinephrine at the presynaptic nerve terminals, increasing concentration and prolonging duration of action of this monoamine at the synaptic cleft (Jain et al., 1990). Secondly, cocaine may directly acts at the postsynaptic effectors (Alburges et al, 1996). According to the suggestion of Trendelenburg and colleagues (1972), the sensitizing effects of low concentration of cocaine, which has a little effect on the neuronal uptake, may indicate some postsynaptic effects. Numerous studies have tried to explain the mechanisms responsible for these effects.

Therefore, the purposes of the present study are to investigate the effect of low doses of chronic cocaine treatment on the responsiveness of β -adrenoceptors to the exogenous catecholamine, epinephrine and non-catecholamine, salbutamol, in the guinea-pig isolated atria and trachea, and to determine the concentration of cocaine in plasma, cardiac and tracheal tissues using high performance liquid chromatography (HPLC). The correlations between the responses and the concentrations of cocaine in plasma, cardiac, and tracheal tissues are also performed.

The results from this study may lead to more understanding of the actions of cocaine-induced supersensitivity in β -adrenoceptors and the mechanisms of its related toxicity to cardiovascular system.