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Combination of opium smoking and hypercholesterolemia augments susceptibility for lethal cardiac arrhythmia and atherogenesis in rabbit

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ABSTRACT

Opium consumption is increasing in some eastern societies, where it is grown. We investigated the effect of opium smoking on plasma atherogenic index and incidence of lethal cardiac arrhythmia, i.e. ventricular tachycardia (VT) and ventricular fibrillation (VF) in rabbits.

Animals were divided into two-, normo- and hyper-cholesterolemic main groups fed with normal or high cholesterol diet prior and during short-term and long-term exposure to opium smoke. Then, isoproterenol (3 mg/kg, i.p.) was injected to induce cardiac ischemia and animals were followed for 3 h for counting of lethal arrhythmia incidence.

Long-term opium smoking significantly increased the plasma atherogenic index. In ischemic hearts, opium smoking along with hypercholesterolemia significantly enhanced the incidence of fatal arrhythmia. This vulnerability was not mediated by changes in QT interval.

These data suggest that opium smoking, especially in hypercholesterolemic conditions, can be a predisposing factor for atherogenesis and lethal arrhythmia.

1. Introduction

Opium dependence is a major public health problem in some parts of the world and it is the most widely abused substance in Iran (INCSR, 2004). It is believed in some quarters that opium consumption has protective/therapeutic effects on cardiovascular diseases such as hypercholestrolemia, hypertension and chest pain. Consequently, use is highly variable (Farahani et al., 2008; Jafari et al., 2009). Although some opioid peptides of myocardial origin have also been shown to play a key role in local regulation of the heart (van den Brink et al., 2003), the influence of opioids on ischemic arrhythmogenesis remains a contentious issue. While some studies suggest either a pro- or anti- arrhythmic role for opioid agonists and antagonists (Sitsapesan and Parratt, 1989; Valtchanova-Matchouganska et al., 2004; Chan et al., 1987), some others complicate the issue by finding lack of effects (Pugsley, 2002). Some studies suggest that blockade of the opioid receptors can be antiarrhythmogenic (Sitsapesan and Parratt, 1989; Murphy and Murphy, 1999). Ischemic hearts are also prone to arrhythmia, and atherogenic substances worsen cardiac ischemia by

Abbreviations: VT, ventricular tachycardia; VF, ventricular fibrillation; NC, normocholesterolemia; HC, hypercholesterolemia; SO, short term opium; LO, long-term opium; ISO, isoproterenol; MAP, mean arterial pressure.

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promoting atherosclerotic plaque formation in coronary arteries. In this regard, cholesterol, especially in LDL form has been found to be among the best known atherogenic substances while its HDL form has anti atherogenic effects.

So far, animal studies related to the effects of opioids on cardiac susceptibility to arrhythmia mostly have involved using morphine and other synthetic opioids and the route of administration has been systemic or oral. Opium is a dark brown colored substance that is obtained from unripe capsules of *Papaver somniferum* L. and it contains morphine and several other alkaloid constituents, including codeine, thebaine and papaverine, which are the most abundant. These alkaloids may vary markedly in their pharmacological actions (Pugsley, 2002). The route of consumption in Iranian users is mostly through smoking (INCSR, 2004) and to our best of knowledge, no study in literature has investigated the effect of opium – especially in the form of smoking – on ischemia induced cardiac arrhythmia. On the other hand, the route of absorption through pulmonary epithelium is probably different with intestine in which gastrointestinal enzymes may affect constituents before absorption. Therefore, to attempt to address these issues, the aim of the present study was to assess the influence of short and long-term exposure to opium smoke inhalation on incidence of lethal arrhythmia – a complication of cardiac ischemia – in normo and hypercholesterolemic rabbits undergoing cardiac ischemia.

2. Materials and methods

This study conformed to the guidelines for conducting animal studies (Ethic committee permission No. 86/123KA-Kerman University of Medical Sciences) and performed on 81 New Zealand White rabbits weighing between 2 and 3.5 kg (purchased from Razi institutes of Iran). Cholesterol from Merck (Germany), Isoproterenol from Sigma (England) and sodium thiopental from Biochemie (Austria) were purchased. Opium consumed in this study was donated by the anti-drug section of Kerman Police (Iran) and based on their information, its origin was Afghanistan.

2.1. Induction of hypercholesterolemia

Animals were randomly assigned to normocholesterolemia (NC) and hypercholesterolemia (HC) series. HC series ($n = 38$) were fed for 2 weeks with cholesterol-enriched diet (2 g of cholesterol mixed with 6% corn oil in each 100 g of rabbit chow) (Kremastinos et al., 2000) and NC series ($n = 43$) fed with usual chow. Half of each series were underwent isoprotrenol injection for induction of myocardial ischemia (see below). Each series were divided to control groups (NC, HC), short term opium groups (NCSO, HCSO) and long-term opium groups (NCLO, HCLO). On the basis of serum lipids, hypercholesterolemia was observed in all animals receiving the cholesterol added regimen.

2.2. Exposing to passive opium smoke

The apparatus for opium smoke production and the method of exposing animals to smoke was introduced elsewhere (Najafipour et al., 2010; Joukar et al., 2010). In brief, the animals were under inhalation of passive opium smoke produced from opium pieces (250 mg each) by an apparatus for 20 min every 6 h for short term (3 days) or long-term (4 weeks) periods. The weight gain of all animal groups was positive during 4 weeks with no significant difference between them showing that the protocol did not change the food and water intake of the animals significantly (Najafipour et al., 2010). At the end of opium smoking period, naloxone (4 mg/kg, ip) was injected to some animals randomly to confirm dependency confirmation. Animals that received naloxone were excluded from the study. The NCLO and HCLO groups, but no NCSO and HCSO groups, showed withdrawal signs such as grooming, head twitch, increased motility, mydriasis, ptosis, and writhing.

2.3. Surgical preparation and experimental protocol

At the end of smoking periods, animals were anaesthetized by sodium thiopental (50 mg/kg, i.p.) and a deep anesthesia level was maintained with 1% halothane in a 30% O_2—69% N_2O mixture during the surgical procedure. After surgery, each animal was left for 1 h to minimize the surgical stress. Then, baseline electrocardiogram (ECG) and arterial blood pressure (BP) were recorded and blood sample was taken for plasma cholesterol and cardiac Troponin I measurement as explained previously (Najafipour et al., 2010; Joukar et al., 2010). Total cholesterol and high density lipoprotein (HDL) levels were measured by routine laboratory methods and total cholesterol/HDL ratio considered as the plasma atherogenic index (Mohammadi et al., 2009). After recording of baseline ECG and BP and also blood sampling, isoproterenol (ISO) 3 mg/kg ip injected for induction of myocardial ischemia (Pinelli et al., 2004) and during following 3 h, BP was recorded continuously and ECG was recorded at the time of arrhythmia appearance. The advantages of ISO-induced ischemia, which occurs as a result of intense inotropic and chronotropic actions of this sympathomimetic drug, compared to physical occlusion of coronary artery, are: non invasiveness and better survival rate of animals after induction of ischemia. In this method, myocardial injury was confirmed based on increase of serum cardiac Troponin I and heart histopathological findings (Najafipour et al., 2010; Joukar et al., 2010). Mean arterial pressure (MAP) was calculated by "MAP = DAP + (SAP − DAP)/3 formula", where DAP is diastolic and SAP is systolic arterial pressure (Joukar et al., 2011).

2.4. Assessment of arrhythmia

Ventricular arrhythmia was assessed according to the guidelines of the Lambeth Conventions for the analysis of experimental arrhythmias (Walker et al., 1988). Reference was made to the blood pressure tracings on Physiograph strip for awareness of arrhythmia. When blood pressure pulsation trace was distorted or started to fall rapidly it was a sign of arrhythmogenesis. At this time the electrocardiograph was started to record ECG. We noted the incidence of lethal arrhythmia as the number of ventricular tachycardia (VT) and ventricular fibrillation (VF) occurrences (VT, four or more consecutive ventricular premature beats and VF, inability to distinguish individual QRS complexes). Both of these variables