Toxicology and Applied Pharmacology 262 (2012) 60–69

Contents lists available at SciVerse ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

Acute alteration of cardiac ECG, action potential, I_{Kr} and the human ether-a-go-go-related gene (hERG) K^+ channel by PCB 126 and PCB 77

Mi-Hyeong Park, Won Sun Park, Su-Hyun Jo *

Department of Physiology, Institute of Bioscience and Biotechnology, Kangwon National University College of Medicine, Chuncheon 200-701, Republic of Korea

ARTICLE INFO

Article history:
Received 5 March 2012
Revised 16 April 2012
Accepted 17 April 2012
Available online 28 April 2012

Keywords:
Action potential
ECG
hERG channel
PCB 126
PCB 77
Short QT syndrome

ABSTRACT

Polychlorinated biphenyls (PCBs) have been known as serious persistent organic pollutants (POPs), causing developmental delays and motor dysfunction. We have investigated the effects of two PCB congeners, 3,3′,4,4′-tetrachlorobiphenyl (PCB 77) and 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126) on ECG, action potential, and the rapidly activating delayed rectifier K^+ current (I_{Kr}) of guinea pigs' hearts, and hERG K^+ current expressed in *Xenopus* oocytes. PCB 126 shortened the corrected QT interval (QTc) of ECG and decreased the action potential duration at 90% (APD_{90}), and 50% of repolarization (APD_{50}) ($P<0.05$) without changing the action potential duration at 20% (APD_{20}). PCB 77 decreased APD_{20} ($P<0.05$) without affecting QTc, APD_{90}, and APD_{50}. The PCB 126 increased the I_{Kr} in guinea-pig ventricular myocytes held at 36 °C and hERG K^+ current amplitude at the end of the voltage steps in voltage-dependent mode ($P<0.05$); however, PCB 77 did not change the hERG K^+ current amplitude. The PCB 77 increased the diastolic Ca^{2+} and decreased Ca^{2+} transient amplitude ($P<0.05$), however PCB 126 did not change. The results suggest that PCB 126 shortened the QTc and decreased the APD_{90} possibly by increasing I_{Kr}, while PCB 77 decreased the APD_{20} possibly by other modulation related with intracellular Ca^{2+}. The present data indicate that the environmental toxicants, PCBs, can acutely affect cardiac electrophysiology including ECG, action potential, intracellular Ca^{2+}, and channel activity, resulting in toxic effects on the cardiac function in view of the possible accumulation of the PCBs in human body.

Introduction

Cardiovascular diseases still remain the leading cause of death in the industrialized world, although a slight decline has been observed during the last decade. For decades, it has been known that POPs constitute important risk factors for future development of cardiovascular disease (Kannel and Larson, 1993). It has been shown that a significant relationship between levels of polychlorinated biphenyls (PCBs) in breast milk and rate of fish consumption in women of Mohawk, which were a traditional fish-eating community at Akwesasne (Fitzgerald et al., 2004). Average PCBs levels in the Mohawks remain higher than those levels found in the overall US population lacking unusual PCB exposure (DeCaprio et al., 2005). Data from NHANES and studies of a native American population have shown the evidence for association between serum level s of POPs and diabetes and cardiovascular disease (Codru et al., 2007; Goncharov et al., 2008).

PCBs are a family of bicyclic chlorinated aromatic hydrocarbons composed of 209 possible congeners. As PCBs were used widely in many common products and in industrial applications such as electrical insulating fluids and heat-exchange fluids, PCBs are one of the most ubiquitous environmental toxicants worldwide, with reported epidemiological evidence for reproductive and neurocognitive anomalies in humans. Accumulating epidemiological evidence reveals that people exposed to high levels of dioxins and dioxin-like compounds, such as coplanar PCBs, have increased risk of developing diabetes mellitus and cardiovascular diseases (Cranmer et al., 2000; Steenland et al., 1999). PCBs have been shown to be important factors for development of hypertension (Ha et al., 2009), and strokes (Dalton et al., 2001; Gustavsson and Hogstedt, 1997). These cardiovascular diseases can be associated with excess mortality of capacitor manufacturing workers exposed to PCBs (Gustavsson and Hogstedt, 1997).

3,3′,4,4′,5-Pentachlorinated biphenyls 126 (PCB 126), a dioxin-like coplanar PCB, has been known to induce the changes in human endothelial cells that are characteristic for endothelial dysfunction in human hypertension and the transcription of genes important for vascular function in human endothelial cells can be elevated by increased estrogen levels (Andersson et al., 2011). Other coplanar PCBs, 3,3′,4,4′-tetrachlorobiphenyl (PCB 77), bind to the aryl hydrocarbon receptor (AhR) in endothelial cells, showing the potential to induce the expression of proinflammatory cytokines including IL-6, which has been shown to be powerful independent risk predictor of cardiovascular diseases (Wang et al., 2010). Also, PCB 77 has been shown to cause up-regulation of cytochrome P450 1A1 (Toborek et

* Corresponding author at: Department of Physiology, Kangwon National University School of Medicine, Hyoja-Dong, Chuncheon 200-701, Republic of Korea. Fax: +82 33 255 8809.
E-mail address: suhyunjo@kangwon.ac.kr (S.-H. Jo).

0041-008X/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.taap.2012.04.019

al., 1995). The PCB 77 can induce expression of MCP-1, a critical regulator of early stages of atherosclerosis by AhR, as well as p38 and JNK MAPK pathways, indicating that the risk factors for the development of atherosclerosis, the primary cause of heart disease and stroke, include environmental exposure to PCB 77 (Majkova et al., 2009).

The human ether-a-go-go related gene (hERG) channel plays an important role in cardiac action potential repolarization as a main component of the rapid delayed rectifier K^+ current (I_{Kr}) (Warmke and Ganetzky, 1994). The hERG channel comprises four identical subunits and each subunit is predicted to have a typical voltage-gated potassium channel region with six transmembrane segments (S1–S6) and N- and C-terminal domains (Warmke and Ganetzky, 1994). The unusual kinetics of hERG are compatible with its function in cardiac repolarization: in the ascending phase of the action potential, little outward current flows through hERG during depolarization as a result of slow activation and simultaneous fast inactivation (Zhou et al., 1998). Mutations that reduce hERG conductance or surface expression may cause congenital long QT syndromes (LQTs) (Hedley et al., 2009). However, the channels can be inhibited by wide variety of drugs of different classes and structurally diverse small molecules, potentially causing a prolongation of action potential duration (APD) in ventricular myocytes, an acquired form of LQTs, arrhythmias, and sudden death, which is a major problem in drug development (Boukharta et al., 2011). Also, hERG defects have also been linked to other diseases, such as stress-mediated arrhythmias, diabetes, and myocardial ischemia induced arrhythmias (Guan and Yang, 2007).

There is no report about the electrophysiological effect of PCB 126 or PCB 77 on the acute cardiac function although there are several reports showing the high-risk of cardiovascular disease and endothelial cell changes induced by PCBs as aforementioned. Thus, the current study was designed to examine whether PCB 126 or PCB 77 could affect the electrical activity of mammalian heart, such as hERG channels, shape of action potentials (AP), Ca^{2+} transient, electrocardiogram (ECG) by using *Xenopus* oocyte expression assays and guinea pig heart model.

Table 1
Comparison of QTc and heart rates in guinea pig with different PCB 126 exposure conditions (mean ± S.E., $^*P<0.05$).

Group	QTc (s)	Heart rates (beats/min)	n
Control	0.258 ± 0.014	91.34 ± 9.93	6
1 μM/5 min	0.242 ± 0.023	101.36 ± 11.10	6
1 μM/10 min	0.236 ± 0.024	98.26 ± 10.47	6
10 μM/5 min	0.204 ± 0.029*	90.00 ± 12.49	5
10 μM/10 min	0.201 ± 0.028*	89.57 ± 12.54	5

Materials and methods

Ventricular myocyte isolation. Single ventricular myocytes were isolated from each guinea pig heart using a method described previously (Jo et al., 2001). Briefly, guinea pigs (300–500 g) were anesthetized with pentobarbital (~50 mg/kg, i.p.) and the heart was quickly excised. The heart was retrogradely perfused at 37 °C with a solution A containing 750 μM Ca^{2+} and a Ca^{2+}-free solution A followed by an enzyme solution. The enzyme solution contained solution A,

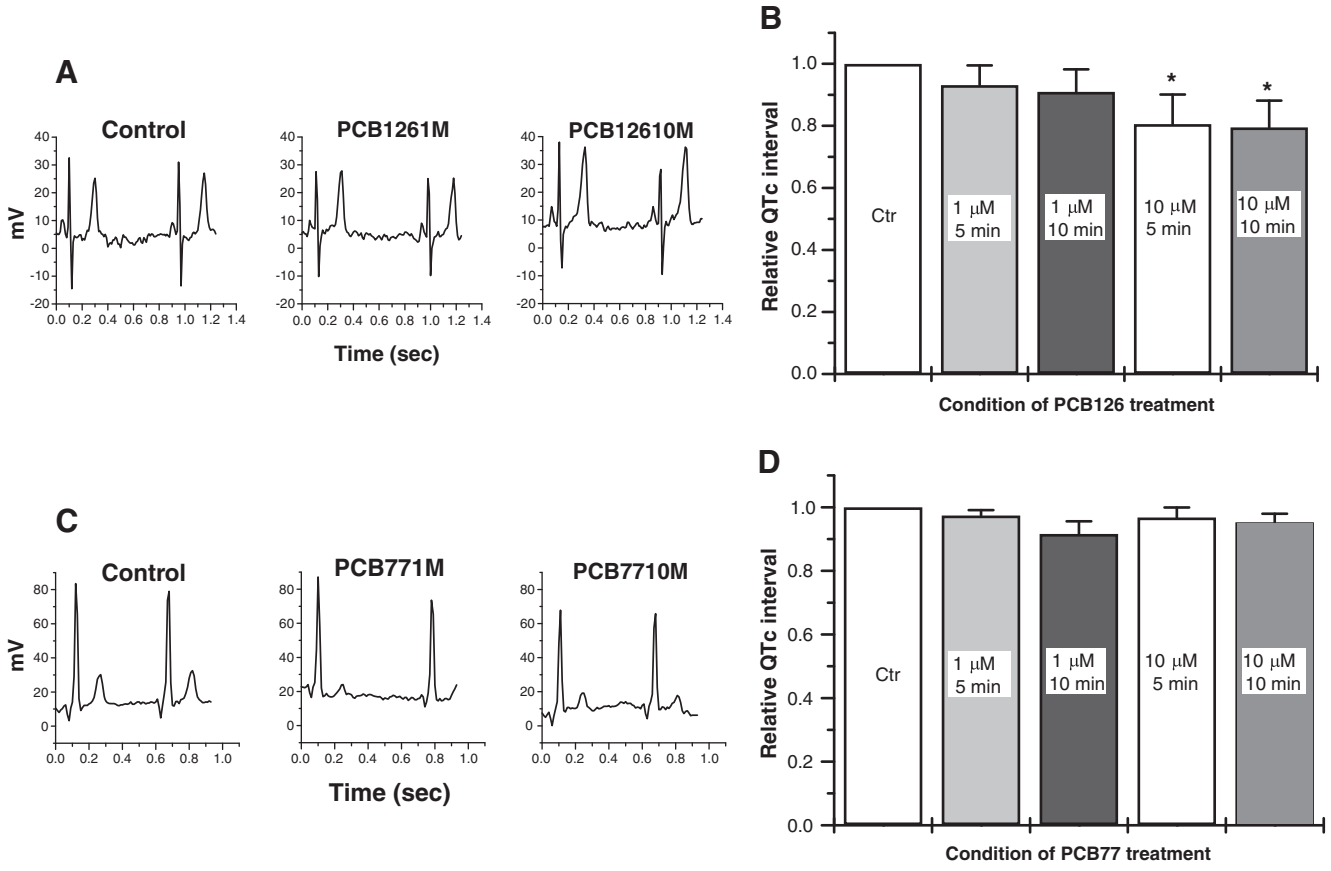

Fig. 1. Effects of two environmental hormone, 3,3′,4,4′5-pentachlorobiphenyl (PCB 126) and 3,3′,4,4′-tetrachlorobiphenyl (PCB 77) on electrocardiogram (ECG) of isolated guinea pig hearts. (A) Representative traces of ECG in the absence of PCB 126 and in the presence of 1 and 10 μM PCB 126 for 10 min. (B) Bar graphs showing the effects of PCB 126 on the corrected QT interval (QT_c) of ECG (n = 5–6). (C) Representative traces of ECG in the absence of PCB 77 and in the presence of 1 and 10 μM PCB 77 for 10 min. (D) Bar graphs showing the effects of PCB 77 on the QT_c of ECG (n = 5–6). $^*P<0.05$.