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Protective Effect of Diltiazem and Fenofibrate Against Ischemia-reperfusion Induced Cardiac Arrhythmias in the Isolated Rat Heart.

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Introduction

Fenofibrate is a peroxisome proliferator-activated receptor (PPAR)-α activator, that lowers triglycerides.

It also influences cytochrome P-450 (CYP-450) dependent arachidonic acid (AA) metabolism.

CYP-450 metabolizes AA to epoxyeicosatrienoic acids (EETs)

EETs are synthesized in the renal, vascular and cardiac tissues.

(Huang et al., 2007; Campbell et al., 1996; Campbell and Falck, 2007;

Introduction

EETs have coronary dilating, cardiac and renal protective properties.

Fibrates have shown to possess similar properties due to its CYP-450 inducing action and increasing the endogenous EETs production.

Larsen et al., 2005; Campbell and Fleming 2010;Fleming 2008).

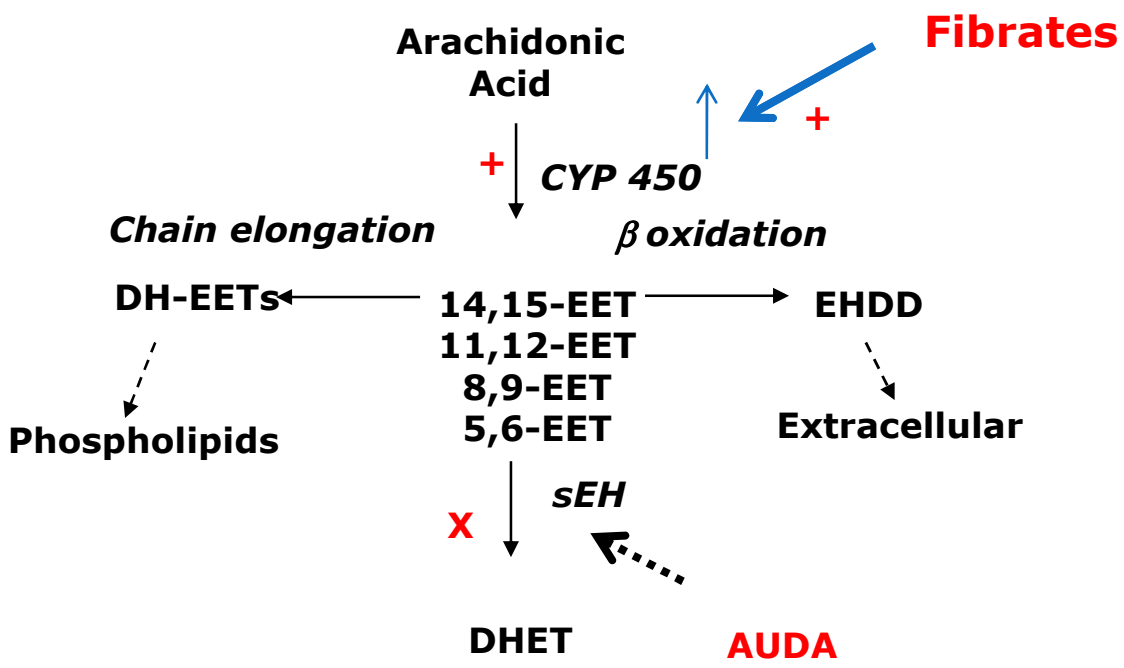
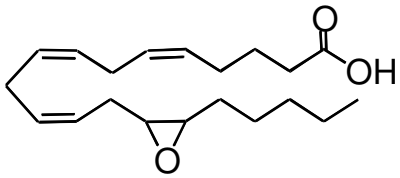
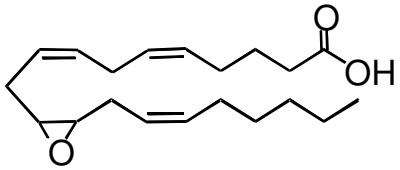

Arachidonic
Acid
Fibrates
+
+
CYP 450
Chain elongation
β oxidation
DH-EETs
14,15-EET
11,12-EET
8,9-EET
5,6-EET
EHDD
Phospholipids
Extracellular
sEH
X
DHET
AUDA

Figure 1

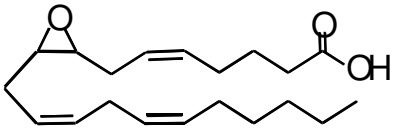
Agonists



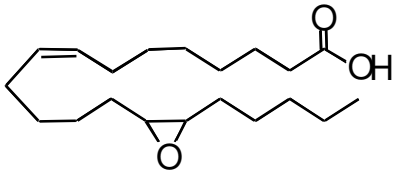
14,15-EET



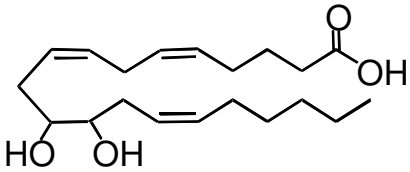
11,12-EET



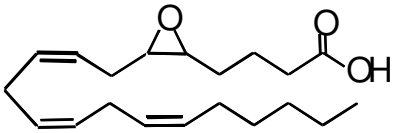
8,9-EET



14,15-EE8ZE

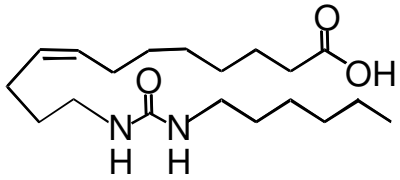


11,12-DHET



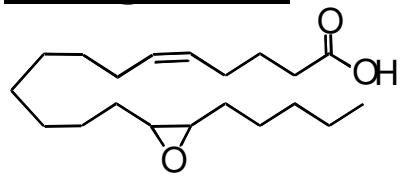
5,6-EET

Agonist/sEH inhibitor

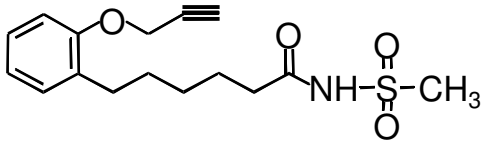


14,15-Urea-E8ZE

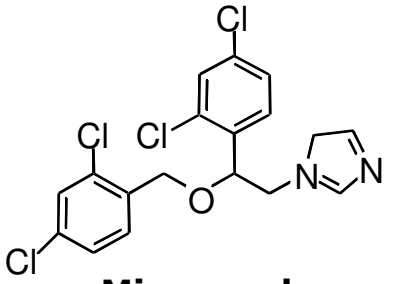
Antagonists



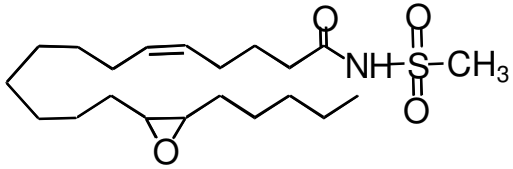
14,15-EE5ZE



MS-PPOH



Miconazole



14,15-EE5ZE-mSI

Figure 2

Introduction

Several reported physiological functions of EETs include:

dilatation of coronary, renal and cerebral arteries and anti-inflammatory effects in vascular tissue (Campbell and Falck, 2007; Larsen et al., 2007; Spector and Norris, 2007 and Bukhari et al.,2011).

up-regulation of sEH expression, leading to a decrease in EET availability, with the development of left ventricular (LV) Dysfunction (Monti et al., 2008)

Recent in vitro/in vivo studies in isolated cells and transgenic animal models have revealed potent cardiac protective effect of EETs and markedly reduce I/R induced heart injuries. (Nithipatikom and Gross 2010; Denga et al., 2010; Batchu et al., 2011).

Rationale of our study

Fibrates have previously been reported to increase CYP epoxygenase activity , EETs production and anti-hypertensive effects (Huang et al., 2007).

Increasing EETs bioavailability, by inhibition of soluble epoxide hydrolase (sEH), is a little explored but promising pharmacological target

Several in-vitro studies have shown the cardiac protective effect of EETs but studies related to increased production of endogenous EETs by fibrates and its cardiac protective effects are lacking (Nithipatikom and Gross 2010; Denga et al., 2010; Batchu et al., 2011)..

Aim of our study

The aim of our study was to investigate protective effect of fenofibrate (EETs inducer) against ischemia and re-perfusion (I/R) induced cardiac arrhythmias in isolated rat hearts.

Methods

- **Treatment protocol:**
- Male Wistar rats (250-350 g) were didvided into two groups.
- **Group 1** served as a control and was treated with vehicle only (peanut oil).
- **Group 2** was treated with fenofibrate (100 mg/kg p.o) for 5 days.
- One hour After the administration of the last dose (5th dose) of fenofibrate, rats were anethetized with thipopental, hearts were isolated for mounitng on langendorff apparatus as described below.

Method: Ischemia-reperfusion-induced arrhythmia

- Isolated Hearts were perfused with Krebs-Henseleit solution gassed with carbogen and at constant flow of 10 ml/ min (37^0C.)
- Isometric contractions recorded from left ventricle by Harvard UFI transducer.
- Perfusion pressure was monitored with a pressure transducer.
- Surface electrical records were obtained from electrodes placed on the right atrium and apex of left ventricle.
- All signals were fed into Harvard transducer interfaces and then into PowerLab/8sp(ADInstruments).
- All hearts were stabilized for 15 min. Coronary artery ligature was tightened and released after 10 min and Ventricular arrhythmias recorded for 30 min post-ligation.

Xi et al., 2009

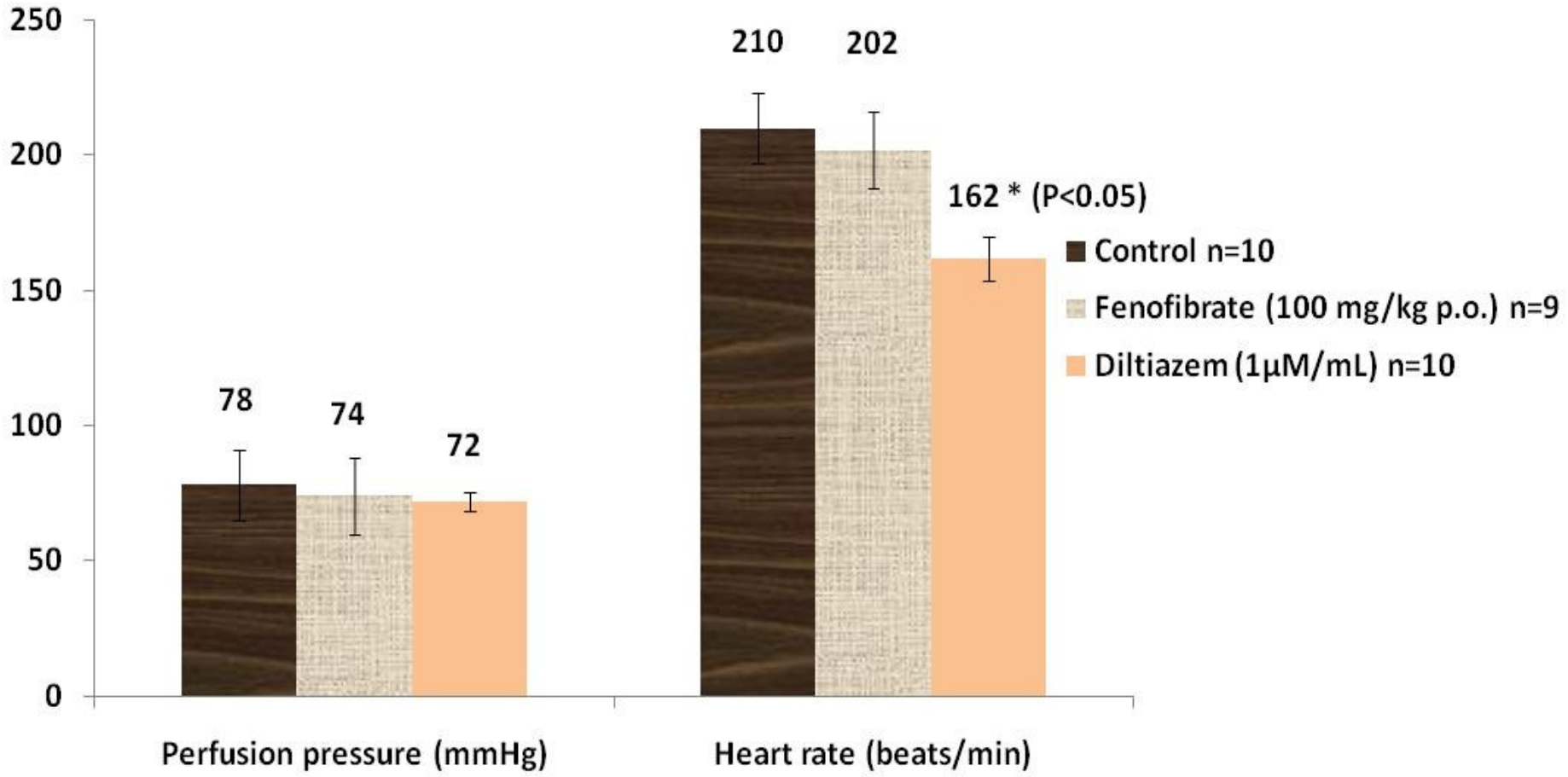
Method

Following parameters were quantified during the ligation (10 min) and after release of ligature for 30 minutes:

1. Number of premature ventricular contractions (PVCs)
2. Incidence and duration of ventricular tachycardia (VT)
3. Incidence and duration of ventricular fibrillation (VF)
4. Perfusion pressure

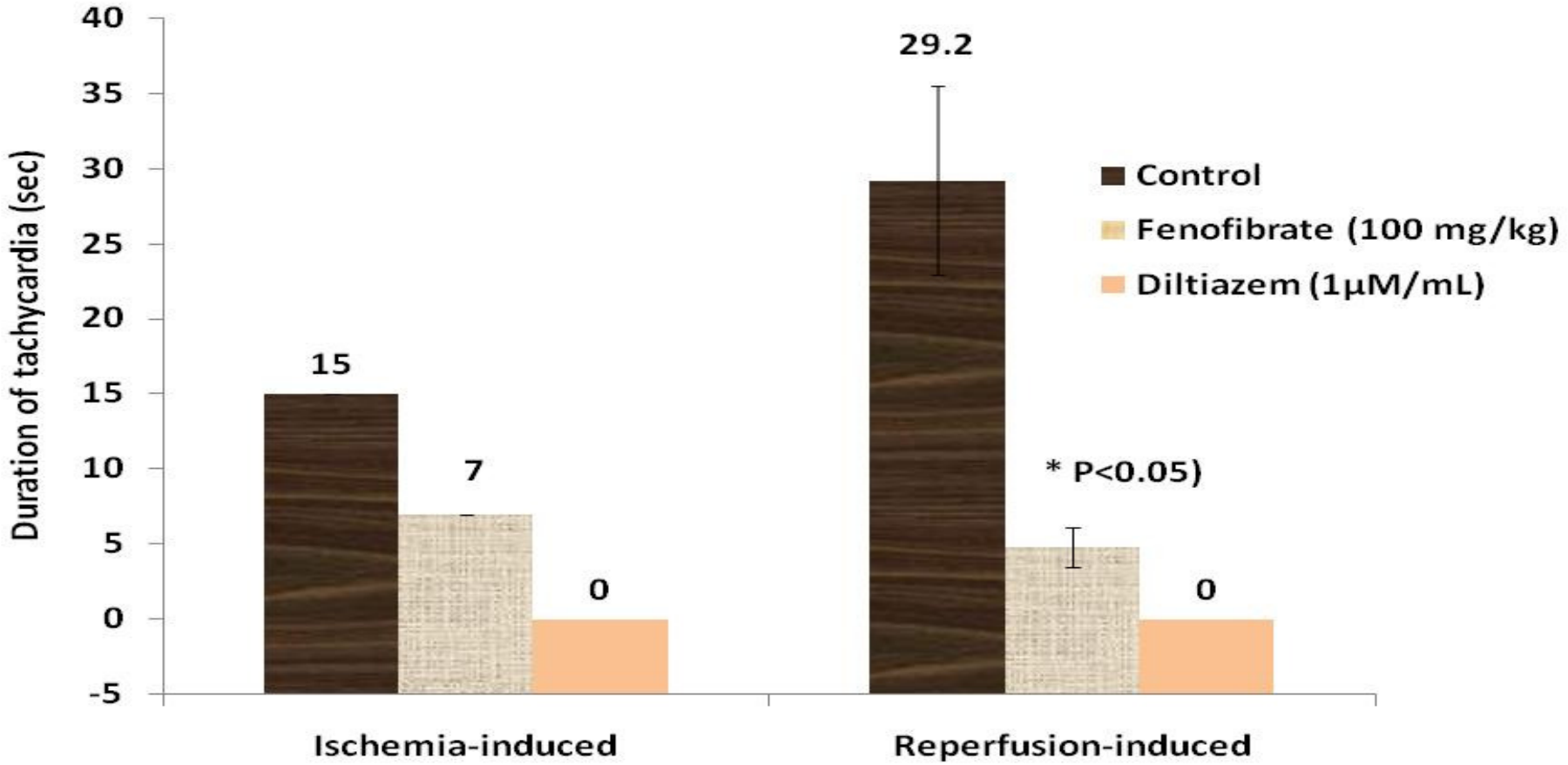
Results

Figure 1. Comparison of perfusion pressure and heart rate in control and fenofibarte treated animals



Results

Figure 2. Effect of fenofibrate on Ischemia-reperfusion induced ventricular tachycardia



Results

Figure 3. Effect of Fenofibrate on Ischemia-reperfusion induced ventricular fibrillation

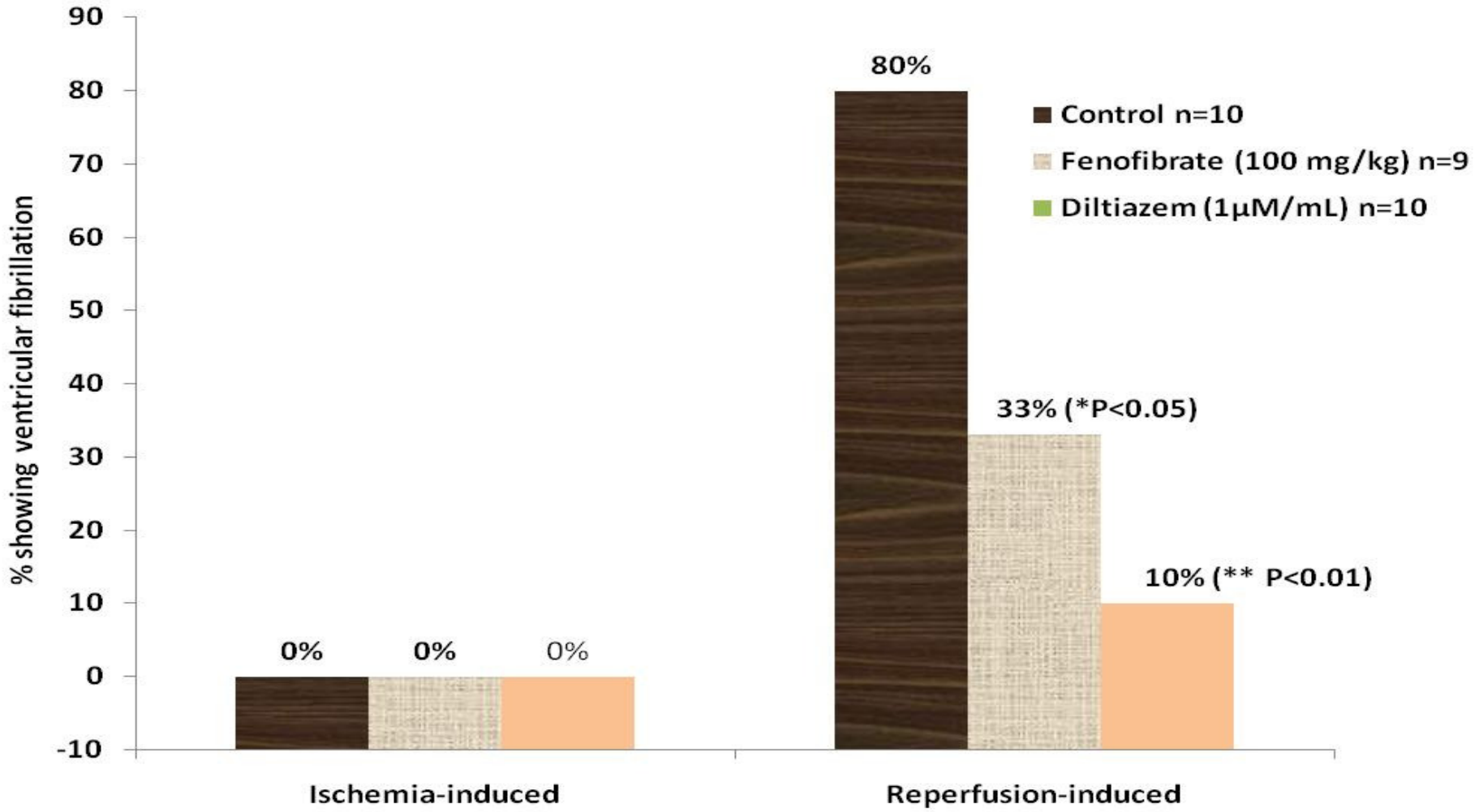


Table: Summary of the Effects of Fenofibrate and Diltiazem on ischemia-reperfusion induced cardiac arrhythmia in isolated rats heart.

	Ischemia-induced				Re-perfusion-induced			
			(incidence %)				(incidence (%)	
Group	**VPC (counts)**	**VT (duration in sec)**	**VT**	**VF**	**VPC (counts)**	**VT (sec)**	**VT**	**VF**
Control (n=10)	47 ± 16.5	15 (n=2)	20%	_	223.2 ±110	**29.2 ± 6.3**	40%	**80%**
Fenofibrate 100 mg/kg (n= 9)	54.2 ± 22	7 (n=1)	11.1%	_	136.8±22	**4.8 ±1.3***	44.5%	**33.3%***
Diltiazem (1 µM/mL) n= 10	_	_	_	_	_	_	_	**10 %****

***P<0.05, **P<0.01; VPC= ventricular premature counts, VT= ventricular tachycardia, VF= ventricular fibrillation**

Discussion and conclusion

- Fenofibrate significantly ($P<0.05$) decreased the number of PVCs, the incidence of VF and the duration of VT in isolated rat hearts.
- Fenofibrate induces cytochrome P-450 (CYP-450) dependent arachidonic acid (AA) metabolism to EETs.
- Fibrates have previously been reported to increase CYP epoxygenase activity , EETs production and anti-hypertensive effects (Huang et al., 2007).
- The cardiac protective effect of fenofibrate may have occurred due to enhanced production of endogenous EETs.
-

Discussion and conclusion

- **EETs function as EDHF and dilate coronary arteries (Campbell et al., 1996), however in our study no significant difference was observed in the Perfusion pressure of control and fenofibrate treated animals.**

- **Diltiazem produced marked anti-arrythmic effect , indicating the role of calcium channels in the I/R-induced arrythmia.**

Conclusion

The findings from our pilot study indicate that fenofibrate protects ischemia-reperfusion-induced arrhythmia in isolated rat hearts.

Further studies are underway in our lab to further explore the role of EETs in the observed cardiac protective role of fenofibrate in rats.

Our ongoing research focused at exploring the effect of chronic treatment of fibrate on high fat diet induced cardiovascular and metobolic disorders in rats.

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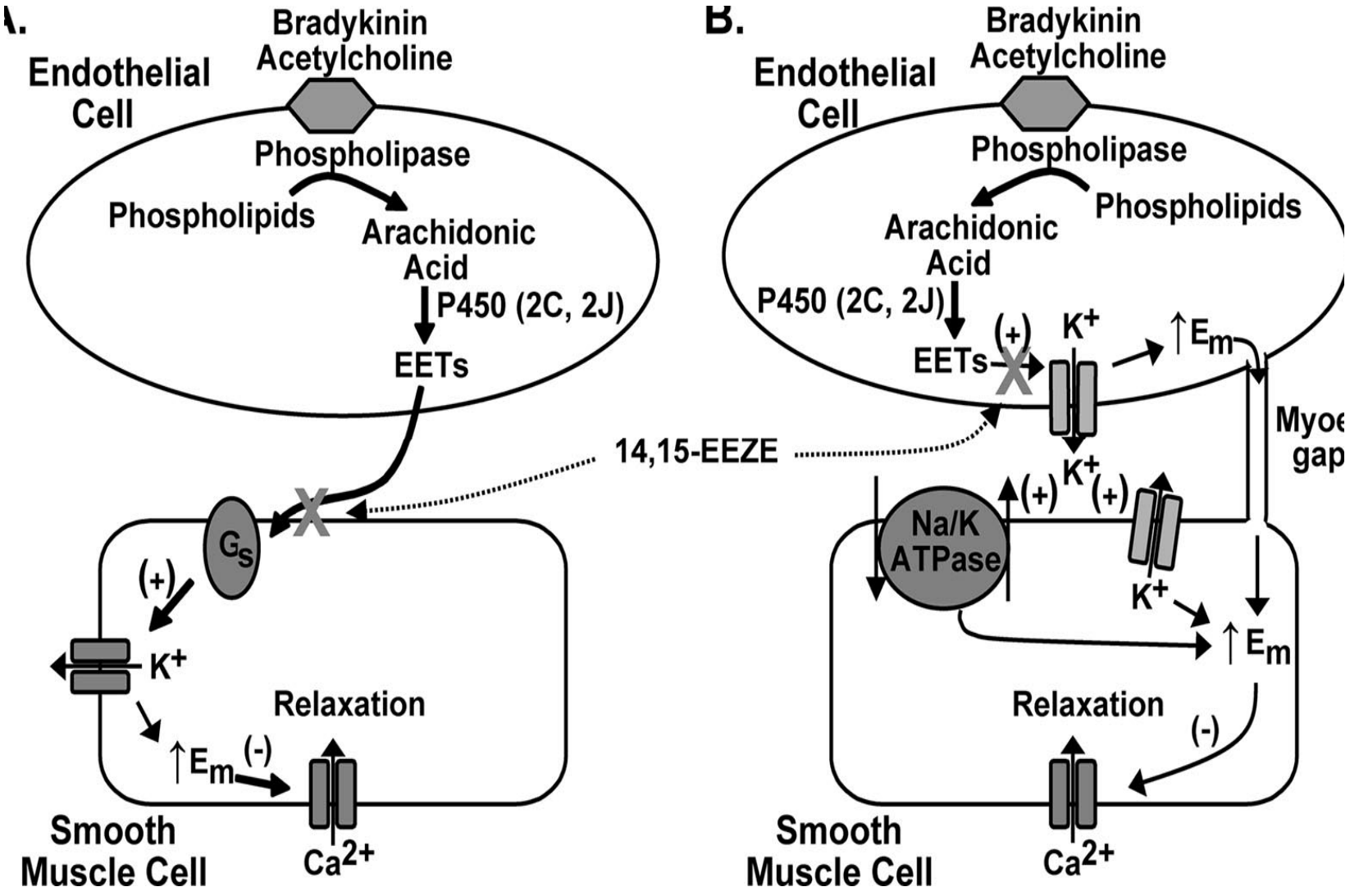
Thank you

Molecular mechanism of EETs



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