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Effect of New Thiophene Derivatives on Rat Heart

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Newer chemical entities (NCE) of thiophene class were synthesized by Gewald reaction and tested for influence on myocardial function in albino rats. Two potent antioxidant possessing agents (NCE-I and NCE-II) were selected for the study using modified Langendorff's method. Different concentrations of NCEs were evaluated for their effect on ischemia/reperfusion injury in isolated rat heart preparation by measuring the developed tension and resting tension. The results indicated that NCE-I had improved the functioning of ischemic myocardium upon reperfusion while NCE-II did not exhibit any beneficial effect on the functioning of cardiac muscle subjected to ischemia/reperfusion injury.

Key Words: Thiophene derivatives, 1,1-Diphenyl-2-picryl hydrazyl, Ischemia/Reperfusion injury, Cardioprotective.

INTRODUCTION

Heart diseases are one of the major causes for most of the mortalities in developed countries[1]. Although, in the last few decades, there has been a revolutionary change in the therapy of cardiac diseases but still mortality occurs mainly due to the ischemia related complications. Major damage occurs due to the interaction of host cell with the free radicals generated during ischemia. Previous evidences indicate that antioxidants are effective in limiting the actions of free radicals, however, their role on the functioning of myocardium is not clear[2].

Thiophenes are heterocyclic compounds consisting of cyclopentene ring structures[3]. They were reported to possess analgesic, antipyretic, anti-inflammatory, spasmolytic, antioxidant, antifungal, antibacterial activities[4,5]. Besides, thiophene 3-N-substituted compounds were found to exert α-antagonist action and could be potential agents in the treatment of hypertension[6]. Hence the present investigation was undertaken to study the effect of newer chemical entities of thiophene class on isolated rat heart preparation.

EXPERIMENTAL

Animals (albino rats of 150–250 g) were maintained under standard laboratory

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conditions prior to the experiment. The experiments were conducted in CPCSEA (Committee for the Purpose of Control and Supervision of Experiment on Animals, Chennai, India) approved animal house. New chemical entities (NCE-I and NCE-II) were synthesized at the Research Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy, Bangalore and the compounds have been patented (Patent No. 782/MAS/2001).

A stock solution of 1,1-diphenyl-2-picryl hydrazyl (DPPH) was prepared in methanol (25 μL/mL); the absorbance was recorded at 517 nm. The percentage inhibition of the test compound was measured by comparing the absorbance with the blank solution[7].

The myocardial function was recorded using the modified Langendorff's apparatus[8]. The isolated rat hearts were subjected to 15 min of global no flow ischemia followed by reperfusion for 15 min and the extent of injury was analyzed. The treated groups of hearts were perfused with Krebs-Henseleit solution containing different concentrations of NCE-I, NCE-II and the effect on the functioning of heart was evaluated. Resting tension (basal tension required for recording the contraction of the heart, *i.e.*, 2 g) and developed tension (tension developed during the contraction at the optimum resting tension of the heart and is a function of the work done by isolated heart) were recorded to evaluate the functioning of myocardium[9]. The results were statistically analyzed by ANOVA followed by Dunnett's multiple comparison test.

The antioxidant potency of the thiophene derivatives was evaluated for free radical (DPPH) scavenging activity. The results indicated that NCE-I and NCE-II had exhibited the antioxidant activity to an extent of 93% and 97% at 100 μg and 300 μg respectively (Fig. 1).

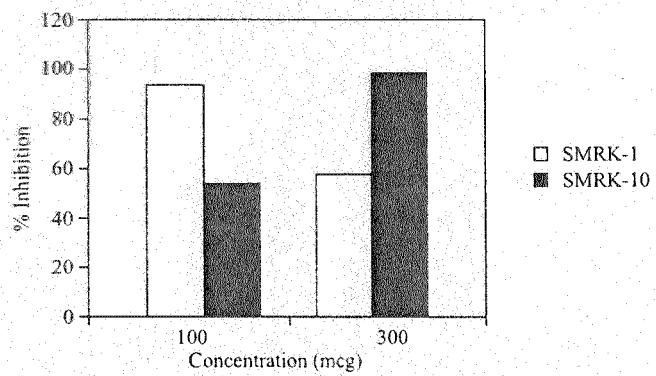
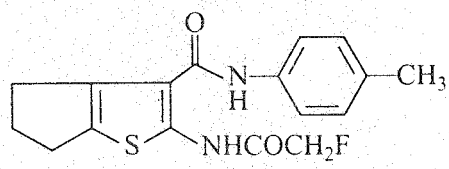


Fig. 1. Free radical (DPPH) scavenging activity

Resting tension during normal perfusion of isolated rat hearts did not change; however, change in the resting tension was observed during post ischemic (reperfusion) period. When the normal heart was perfused with different concentrations of NCE-I and NCE-II, NCE-I at a concentration of 0.1 and 0.3 μM and NCE-II at 3 ηM had induced a significant increase in the recovery of developed tension ($P < 0.05$) during reperfusion period. However, the other doses of NCE-I and NCE-II did not affect the resting and developed tension significantly.

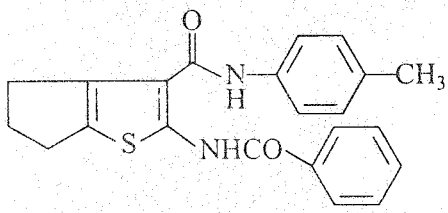
The post-ischemic analysis indicated a significant ($P < 0.05$) variation in the resting tension and developed tension compared with normal heart. When NCE-I and NCE-II were perfused throughout the experiment, NCE-I at 0.1 and 0.3 μM had significantly ($P < 0.05$)) protected the heart from the increase in the resting tension and increased the recovered developed tension. NCE-II at the tested doses did not produce similar action, although NCE-II at 3 and 10 ηM significantly ($P < 0.05$) elevated the resting tension (Table-1).

NCE-II



2-Benzoyl amino-3-(N-*p*-tolyl carboxamido)-4,5-trimethylene thiophene

NCE-I



2-ω-Fluoroacetamido-3-(N-*p*-tolyl carboxamido)-4,5-trimethylene thiophene

TABLE-1
EFFECT OF NCE-I AND NCE-II ON NORMAL AND ISCHEMIC HEART

Group	Parameters	Control	Concentration of NCE-I			Concentration of NCE-II		
			0.1 μM	0.3 μM	1 μM	1 ηM	3 ηM	10 ηM
Normal heart	Developed tension	12.66 ± 1.43	17.30 ± 0.89*	27.84 ± 2.84**	7.19 ± 12.27	3.24 ± 7.96	18.99 ± 2.15*	10.09 ± 10.27
	Resting tension	20.19 ± 0.02	12.32 ± 1.81*	11.73 ± 2.01*	17.12 ± 0.34	16.95 ± 0.62	10.27 ± 2.01*	19.01 ± 0.38
Ischemic heart	Developed tension	7.66 ± 1.53†	18.40 ± 4.05*	35.76 ± 6.89**	11.57 ± 4.84	11.81 ± 2.54	8.22 ± 1.66	11.55 ± 3.67
	Resting tension	69.7 ± 7.63††	30.41 ± 4.63*	31.25 ± 5.12*	67.70 ± 10.37	61.87 ± 11.96	92.70 ± 11.45	75.00 ± 20.62

Values are mean ± SEM, *$P < 0.05$, **$P < 0.01$ compared with control, †$P < 0.05$, ††$P < 0.01$ compared with normal heart, n = 6.

RESULTS AND DISCUSSION

The present investigation indicates that NCE-I at the concentration of 0.1 and 0.3 μM improves the functioning of ischemic myocardium. Similar results were not observed for NCE-II (1, 3 and 10 ηM), although both the agents exerted an antioxidant activity by DPPH method.

The oxygen-free radicals generate intracellularly and extracellularly in myocardium and endocardium during ischemia and reperfusion causes lipid peroxidation of the cell membrane and intracellular Ca^{2+} overload, which are responsible for mechanical and metabolic damage. Antioxidants could be the potential agents for the cardioprotective activity[10].

Myocardial function of NCEs was evaluated by measuring the resting tension and developed tension; elevation in resting tension indicates the damage to cardiac musculature while increase in recovered developed tension shows an improvement in the myocardial contraction. Since only NCE-I enhances the functioning of cardiac muscle, the mechanism might have not only involved the antioxidant activity.

Earlier studies carried on Org 9731 (benzo-thiophene derivative) indicated a positive inotropic effect associated with an increase in intracellular Ca^{2+} transient. The results further revealed that Org 9731 increased cardiac contractility mainly through the accumulation of cAMP and also by increasing the responsiveness of myofibrils to Ca^{2+} ions[11]. Similar type of Ca^{2+} sensitizing effect was reported with Org 30029 (thiophene carboxidamide derivative) and the increased availability of Ca^{2+} was attributed for the improvement in the myocardial function[12]. In our study, NCE-I exhibited a significant positive inotropic effect by decreasing the resting tension and increasing the developed tension. The response might be mediated through the receptor to increase the intracellular Ca^{2+} transient; however, the NCE-II did not show similar effect on ischemic heart, could be due to the inability of the compound to produce the intrinsic activity from the receptor.

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