TÜBİTAK

Original Article

Turk J Med Sci
2010; 40 (2): 249-256
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E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-0808-8

Effects of adenosine A1 receptor agonist CCPA and antagonist DPCPX on ischemia/reperfusion-induced arrhythmias in rats*

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Aim: Adenosine has been commonly used to treat supraventricular tachycardia in clinics. However, there are only a few studies on the effects of adenosine on ischemia or reperfusion induced arrhythmia and they conflict with the results of the present study. During this study, we aimed to clarify the effect of adenosine on ischemia-reperfusion induced arrhythmia.

Materials and methods: Left coronary artery was ligated for 6 min and it was released for 15 min to produce reperfusion. A1 adenosine agonist CCPA (2 Chloro - N6 – Cyclopentyl-adenosine), and A1 selective antagonist DPCPX (8 – Cyclopentyl - 1,3 -dipropylxanthine) in 5 µg/kg dose alone and in combination were given intravenously before ligation, at the second minute of the ligation and just following the reperfusion.

Results: Adenosine given only at the second minute of the ligation is found to decrease the total duration of arrhythmia observed in the reperfusion stage. DPCPX given in this period is found to block the antiarrhythmic effect of adenosine. Adenosine given after reperfusion and before ligation was not effective in decreasing reperfusion induced arrhythmia.

Conclusion: The time dependent effect of the administration during ischemia and reperfusion was important for the effect of adenosine. The present study showed that antiarrhythmia produced by adenosine is related to the activation of A1 adenosine receptor.

Key words: Ischemia, reperfusion, arrhythmias, adenosine

Sıçanlarda, adenozin agonisti, CCPA, ve antagonisti DPCPX'in iskemi / reperfüzyon ile uyarılan aritmiler üzerine etkisi

Amaç: Adenozin supraventriküler taşikardili hastaların tedavisinde kullanılan etkili bir ilaçtır. Ancak, adenozinin iskemi ve reperfüzyon aritmileri üzerine adsenozin etkisi ile ilgili sadece bir kaç çalışma vardır ve bunlarında sonuçları tartışmalıdır. Bu çalışmada adenozinin iskemi-reperfüzyon aritmileri üzerine etkisinin araştırılması amaçlanmıştır.

Yöntem ve gereç: Sol koroner arter bağlanarak 6 dakika iskemi ve bağ gevşetilerek 15 dakika reperfüzyon yapılmıştır. Bir A1 adenozin reseptor agonisti olan CCPA (2 Chloro - N6 – Cyclopentyl-adenosine) ve anatgonisti, DPCPX (8-Cyclopentyl-1,3-dipropylxanthine), 5 µg/kg dozunda tek ve birlikte iskemiden önce, iskeminin ikinci dakikasında ve reperfüzyonu hemen takiben intravenöz olarak verilmiştir.

Bulgular: Sadece ligasyonun ikinci dakikasında verilen CCPA, 15 dakikalık reperfüzyon boyunca oluşan aritmi süresini azaltmıştır. Bu dönemde verilen adenozin antagonisti, DPCPX, adenozinin bu antiaritmik etkisini ortadan kaldırmıştır. Reperfüzyon sırasında ve ligasyondan önce verilen adenozinin reperfüzyonu takiben oluşan aritmiler üzerine bir etkisi olmamıştır.

Sonuç: İskemi ve reperfüzyon sırasında veriliş zamanı, adenozinin etkisinde önemlidir. Bu çalışma adenozin ile oluşturulan antiaritminin, A1 adenozin reseptorlarının aktivasyonu ile ilgili olduğunu göstermiştir.

Anahtar sözcükler: İskemi, reperfüzyon, aritmiler, adenozin

Received: 08,06.2008 – Accepted: 20.08.2009

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* This study was performed in the Biology Department of the Faculty of Art and Science, Abant İzzet Baysal University, Bolu-Turkey, and supported by a research fund from Abant İzzet Baysal University (03.08.02.182).

Introduction

Adenosine is currently used as an antiarrhythmic agent in infants and children (1). It may exert its action either by both direct effect on potassium conductance and indirect antiadrenergic action (2) or depressing sinoatrial node activity and attenuating atrioventricular nodal conduction (3).

Extracellular levels of adenosine increase under various conditions, such as ischemia, trauma, seizures and inflammation, due to energy demands and ATP metabolism (4). It is known that the concentration of adenosine in the coronary effluent markedly increases following ischemia (5). In most of the experimental models, adenosine receptor stimulation triggers preconditioning against myocardial ischemia in rats (5-7). On the other hand, there are also some studies indicating no preconditioning effect of adenosine against arrhythmia and infarct size (8-10). It has been shown that adenosine reduces infarct size but does not affect the incidence and severity of arrhythmias following ischemia (11). In another study, it has been observed that adenosine given prior to coronary occlusion reduced the ventricular arrhythmias (12). Similarly, this effect was seen when adenosine was given by infusion into the left ventricle (13). Several studies have demonstrated that adenosine reduced the incidence of arrhythmias in the isolated perfused rat heart as well as anesthetized rats subjected to acute myocardial ischemia (14). In a recent study, it has been shown that adenosine A1 receptor agonist (CCPA) alone did not decrease the duration of arrhythmia during ischemia and even induced lethal arrhythmia during reperfusion (15). However, when it is given together with lidocain, it decreases the arrhythmia. The antiarrhythmic effect of adenosine and its agonist in myocardial ischemia and reperfusion is still unclear. The present study aimed to contribute to the debate by investigating the effect of adenosine on the arrhythmias in ischemia and reperfusion.

Materials and methods

Eighty-seven 7- to 8-month-old male Sprague Dawley rats weighing 250-325g were used. The animals were fed a standard laboratory rat food pellet and allowed to drink tap water ad libitum. All animals were treated in adherence to all of the guiding principles in the care and use of animals together with the recommendation from the Declaration of Helsinki.

Rats were anesthetized with thiopental sodium (100 mg/kg) and tracheotomy was performed for artificial respiration. The left carotid artery was cannulated to measure blood pressure with a blood pressure transducer (Biopac System Inc, Goleta, CA, USA, under the authorized distribution of the representative Commat-Ankara/Turkey). After the chest was opened in the fourth intercostal space, the heart was exposed and a loose loop of traumatic silk was placed around the left main coronary artery, approximately 2 mm from its origin. The heart was returned to its place and artificial respiration was performed using a ventilator (0.9 mL/100 g body weight at a rate of 60 strokes/min). The animals were allowed to stabilize for 5 min before coronary ligation. The 6 min of ischemia was followed by 15 min of reperfusion. In this technique, ligation was achieved by tightening the silk by producing a bowknot and reperfusion was produced by pulling the silk through the bowknot.

At the end of the experiment, the live animals were heparinized (500 IU/kg) and the heart was excised out. The left coronary artery was retightened and coronaries were perfused with 10 mL of isotonic NaCl solution and then 2 mL of ethanol for demarcation of the occluded and non-occluded myocardium. The occluded myocardium and nonoccluded myocardium were separated from each other by dissection and then both areas were weighed individually. The percentage of ventricular myocardium under the risk of infarction was determined.

The experiment was designed in 4 main groups: 1 control and 3 drug-treated groups, including CCPA, DPCPX, and CCPA + DPCPX. In the control group, there was no drug treatment; only coronary ligation was performed. Each drug treated group was divided into 3 subgroups as drug given 10 min before ligation, at the 2nd minute of ligation, and following reperfusion. A1 Adenosine receptor agonist (2 Chloro - N6 – Cyclopentyl-adenosine, CCPA), A1 adenosine blocker (8-Cyclopentyl-1,3-dipropylxanthine, DPCPX), obtained from Sigma Chemical Co. Inc., St. Louis, Missouri, USA, under the authorized distribution of the representative Interlab-İstanbul, Turkey, were prepared in physiological saline and

given intravenously in a dose of 5 μg/kg per 100 μL, 10 min before ligation, at the 2nd minute of ligation, and just following reperfusion from tail veins. Adenosine blocker was prepared and given alone or in combination with adenosine in the same dose and protocol similar to adenosine. The dose of adenosine A1 receptor agonist was determined by the preliminary studies in the literature according to its effect on the heart rate. A dose larger than 5 μg/kg caused severe bradycardia and cardiac arrest. All drugs were prepared daily before injection.

Bipolar ECG was recorded using needle electrodes, and blood pressure was measured from the carotid artery by a blood pressure transducer and stored on a computer using the Biopac System. The duration of the arrhythmia and the heart rate were determined from the ECG using BSL Pro 3.7 software of Biopac. The incidence of arrhythmias was analyzed in accordance with the Lambeth Conventions (16), as ventricular fibrillation (VF), ventricular tachycardia (VT), and other types of arrhythmias including extrasystoles, bigeminy, and salvos (VPC). An arrhythmia score was used to indicate the incidence and the duration of arrhythmias, where 0 indicates no arrhythmia, 1 indicates an arrhythmia duration of less than 10 s, 2 indicates an arrhythmia duration of 11 to 30 s, 3 indicates an arrhythmia duration of 91 to 180 s or reversible VF for less than 10 s, 5 indicates arrhythmia duration longer than 180 s or reversible VF for more than 10 s, and 6 indicates irreversible VF or death of the animal.

All data are expressed as mean ± standard error. Differences between groups were calculated using analyses of variance. After analyses of variance (LSD post hoc test), the test groups and the control group were compared by Student's t-test (unpaired). The survival rate and the incidence of arrhythmias were compared by the X^2 method (Fisher's exact test).

Results

ST segment elevation and an increase in QRS amplitude and the heart rate were observed following the coronary artery ligation in all animals. The animals having low blood pressure below 70 mmHg before ligation (one animal) were excluded from the experiment. Three animals in a group that CCPA and an animal that CCPA and DPCPX were given before ligation, in addition to the 4 animals that were supplied with adenosine during ligation died due to severe bradycardia and cardiac arrest associated with low blood pressure below 20 mmHg. There were no significant differences in the risk of infarct area among the groups and the data are not shown.

Blood pressure and heart rate decreased significantly according to the control in the reperfusion period of the drug treated group that was given CCPA before ligation (Tables 1 and 2) ($P < 0.05$). A similar effect of CCPA was not seen when it was given in combination with adenosine A1 selective blocker DPCPX. On the other hand, DPCPX, which was given at the 2nd minute of ligation alone, decreased the blood pressure and it was not effective on the blood pressure in other groups that were given DPCPX before ligation or during reperfusion. DPCPX and CCPA alone, which were given at the 2nd minute of ligation, did not produce any appreciable effect on the blood pressure recorded in the coronary ligation and reperfusion period according to the control as shown in Table 1. The heart rate in the reperfusion period of animals given CCPA at the 2nd minute of ligation was significantly lower than that of the control animals ($P < 0.01$). This decline in the heart rate stopped when the CCPA was given in combination with DPCPX (Table 2).

The arrhythmic period, which was between the start and the end of the arrhythmia in the 15th minute of reperfusion, was not significantly different in the drug treated groups when compared with the control group. CCPA that was given at the 2nd minute of the ligation decreased the score of arrhythmia significantly ($P < 0.05$); it was 1.6 ± 0.56 in the CCPA group and 3.5 ± 0.26 in the control group (Table 3). The duration of ventricular tachycardia (12 ± 6 s in CCPA, 48 ± 10 s in the control group) (Figure 1) and the total arrhythmia (33 ± 14 s in CCPA, 101 ± 50 s in the control group) during reperfusion (Figure 2) were also lower in that group of animals compared with the control group ($P < 0.05$). The combination of CCPA with DPCPX prevented this antiarrhythmic effect of CCPA. There was no observable individual effect of DPCPX on the reperfusion induced arrhythmia given before the ligation, at the 2nd minute of ligation, and during reperfusion.

Table 1. Mean arterial blood pressure in anesthetized rats. Mean ± standard error. *P < 0.05, **P < 0.01; Difference from control.

Group	N	Before Occlusion	Blood Pressure, mmHg							
			Following Occlusion			Following Reperfusion				
			1 min	3 min	5 min	1 min	3 min	5 min	10 min	15 min
Control	8	114 ± 8	84 ± 8	84 ± 11	84 ± 12	90 ± 7	93 ± 11	104 ± 9	117 ± 8	118 ± 9
A1 Adenosine Receptor Agonist, CCPA (Before ligation)	9	114 ± 8	63 ± 9	58 ± 10	62 ± 11	56 ± 10*	75 ± 12	70 ± 13*	78 ± 13**	104 ± 9
A1 Adenosine Receptor Agonist, CCPA (At 2 min of ligation)	8	112 ± 5	89 ± 11	89 ± 14	87 ± 13	73 ± 10	88 ± 12	103 ± 7	98 ± 7	97 ± 8
A1 Adenosine Receptor Agonist, CCPA (Following reperfusion)	8	126 ± 8	89 ± 12	101 ± 12	92 ± 15	79 ± 13	91 ± 16	102 ± 9	102 ± 6	110 ± 8
A1 Adenosine Blocker, DPCPX (Before ligation)	6	120 ± 11	91 ± 12	94 ± 13	95 ± 14	71 ± 16	93 ± 12	101 ± 11	110 ± 6	110 ± 5
A1 Adenosine Blocker, DPCPX (At 2 min of ligation)	8	128 ± 7	92 ± 8	93 ± 11	83 ± 13	72 ± 11	74 ± 13	73 ± 16	84 ± 11*	82 ± 12*
A1 Adenosine Blocker, DPCPX (Following reperfusion)	6	121 ± 5	89 ± 11	89 ± 14	80 ± 17	74 ± 14	81 ± 16	82 ± 13	100 ± 7	103 ± 7
CCPA + DPCPX (Before ligation)	6	118 ± 4	71 ± 8	71 ± 16	70 ± 16	98 ± 11	102 ± 8	99 ± 10	102 ± 10	97 ± 12
CCPA + DPCPX (At 2 min of ligation)	6	125 ± 2	94 ± 11	86 ± 19	88 ± 11	64 ± 11	74 ± 12	77 ± 11	90 ± 11*	91 ± 11*
CCPA + DPCPX (Following reperfusion)	6	114 ± 8	89 ± 11	96 ± 11	98 ± 12	100 ± 14	117 ± 4	122 ± 3	121 ± 7	122 ± 7

Table 2. Heart rate in anesthetized rats. Mean ± standard error *P < 0.05, **P < 0.01; Difference from control.

Group	N	Before Occlusion	Heart Rate Beats /Min							
			Following Occlusion			Following Reperfusion				
			1 min	3 min	5 min	1 min	3 min	5 min	10 min	15 min
Control	8	403 ± 6	399 ± 25	395 ± 24	398 ± 23	372 ± 31	414 ± 33	388 ± 23	400 ± 24	405 ± 24
A1 Adenosine Receptor Agonist, CCPA (Before ligation)	9	366 ± 5	306 ± 1**	302 ± 21**	282 ± 20**	295 ± 34	329 ± 13*	321 ± 12*	326 ± 9*	345 ± 11*
A1 Adenosine Receptor Agonist, CCPA (At 2 min of ligation)	8	387 ± 9	376 ± 15	342 ± 32	330 ± 32	336 ± 38	289 ± 27**	302 ± 22*	312 ± 21**	310 ± 23**
A1 Adenosine Receptor Agonist, CCPA (Following reperfusion)	8	418 ± 4	444 ± 15*	395 ± 30	400 ± 34	384 ± 49	363 ± 31	339 ± 30	387 ± 43	340 ± 24*
A1 Adenosine Blocker, DPCPX (Before ligation)	6	442 ± 7	418 ± 13	424 ± 8	420 ± 5	330 ± 35	367 ± 13	380 ± 17	377 ± 18	394 ± 16
A1 Adenosine Blocker, DPCPX (At 2 min of ligation)	6	440 ± 10	436 ± 12	425 ± 12	428 ± 14	360 ± 40	348 ± 38	334 ± 40	347 ± 27	357 ± 19
A1 Adenosine Blocker, DPCPX (Following reperfusion)	6	436 ± 5	424 ± 18	423 ± 21	426 ± 22	323 ± 41	335 ± 37*	362 ± 36	317 ± 18*	343 ± 22*
CCPA + DPCPX (Before ligation)	6	382 ± 8	364 ± 13	349 ± 15	362 ± 20	436 ± 13	432 ± 17	434 ± 11	436 ± 15	432 ± 12
CCPA + DPCPX (At 2 min of ligation)	8	420 ± 7	428 ± 14	375 ± 49	365 ± 46	445 ± 26	416 ± 17	404 ± 18	409 ± 13	405 ± 15
CCPA + DPCPX (Following reperfusion)	6	379 ± 10	377 ± 14	388 ± 12	396 ± 17	411 ± 7	389 ± 15	406 ± 11	410 ± 11	426 ± 9

Table 3. The incidence and score of arrhythmia after 15 min of reperfusion (mean ± standard error) *P < 0.05, Difference from control.

Group	N	No arrhythmia N / %	Death during reperfusion N / %	Incidence of arrhythmia, n / %				Score of arrhythmia
				VPC	VT	VF	Br	
Control	8	0 / 0	0 / 0	8 / 100	8 /100	0/0	0/0	3.5 ± 0.26
A1 Adenosine Receptor Agonist, CCPA (before ligation)	10	0 / 0	1 / 10	10 / 100	8 / 80	3 / 30	3 / 30	3.6 ± 0.45
A1 Adenosine Receptor Agonist, CCPA (At 2 min of ligation)	8	3 / 37	0 / 0	5 / 62	5 / 62	0 / 0	3 / 37	1.6 ± 0.56*
A1 Adenosine Receptor Agonist, CCPA (Following reperfusion)	9	0 / 0	1 / 11	9 / 100	8 / 89	2 / 22	2 / 22	3.3 ± 0.5
A1 Adenosine Blocker, DPCPX (Before ligation)	7	0 / 0	1 / 14	7 /100	6 / 86	1 / 14	0 / 0	3.1 ± 0.63
A1 Adenosine Blocker, DPCPX (At 2 min of ligation)	8	1 / 12	0 / 0	7 / 87	7 / 87	1 / 12	0 / 0	2.8 ± 0.47
A1 Adenosine Blocker, DPCPX (Following reperfusion)	8	0 / 0	2 / 25	8 /100	7 / 87	0 / 0	0 / 0	3.8 ± 1.8
CCPA + DPCPX (Before ligation)	6	0 / 0	0 / 0	6 / 100	5 / 83	0 / 0	2 / 33	3.0 ± 0.44
CCPA + DPCPX (At 2 min of ligation)	6	2 / 33	0 / 0	4 / 67	4 / 67	0 / 0	0 / 0	2.1 ± 0.7
ACCPA + DPCPX (Following reperfusion)	8	0 / 0	2 / 25	6 / 75	4 / 50	0 / 0	0 / 0	3.7 ± 1.7

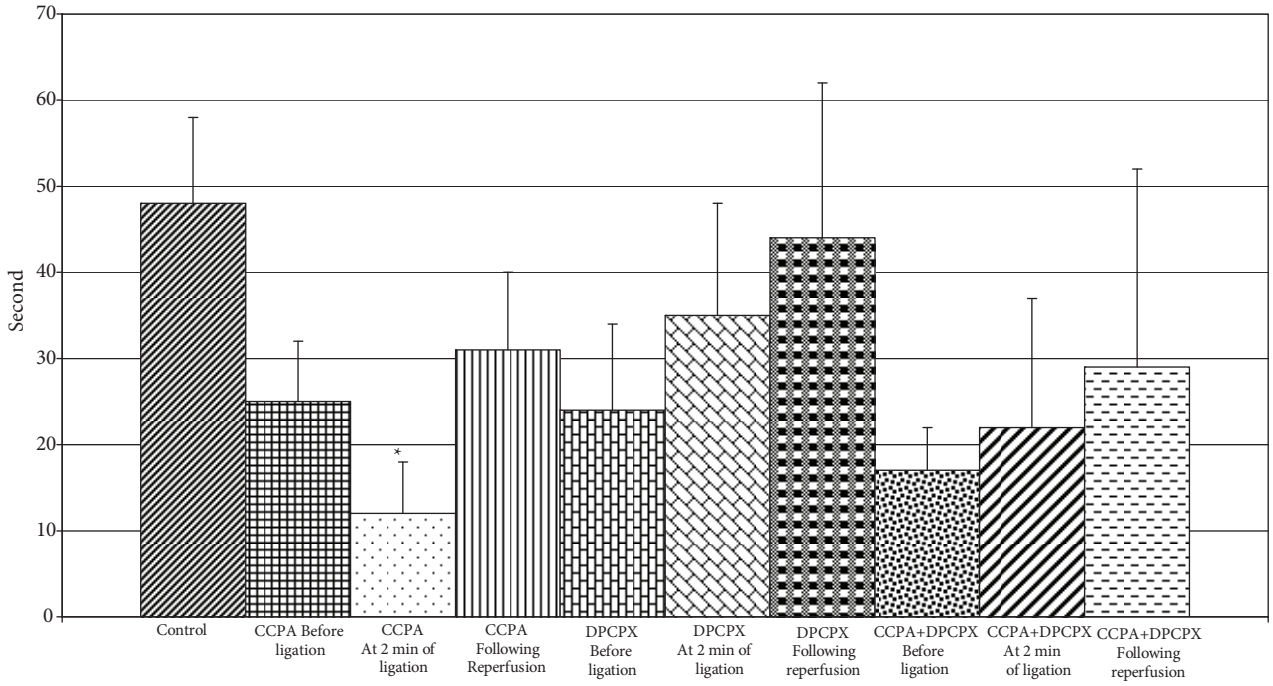

Figure 1. Duration of ventricular tachycardia observed during 15 min of reperfusion P < 0.05.

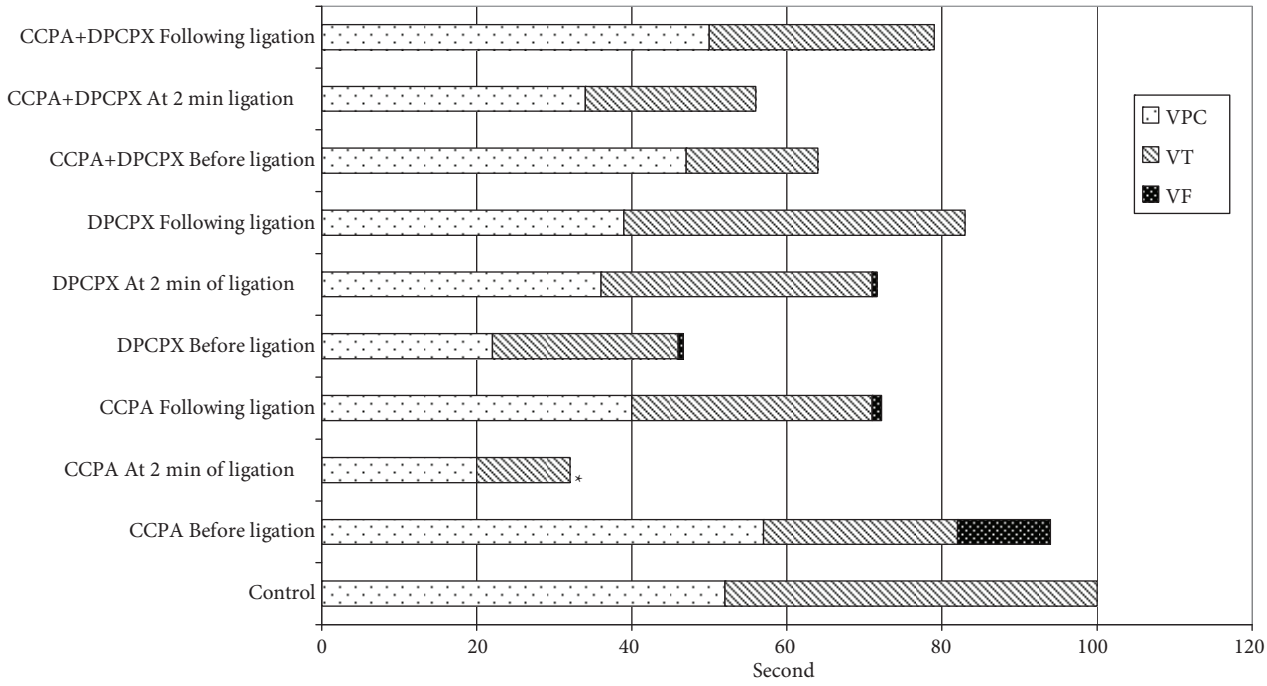

Figure 2. The type and duration of arrhythmias during 15 min of reperfusion $P < 0.05$; difference of total arrhythmia from control.

The incidence of arrhythmia in the 15th minute of reperfusion changed with the treatment of CCPA or DPCPX alone or in combination (Table 3). The risk of an infarct zone in the drug treated groups did not change with respect to the control group and it was above 40% in all groups of animals.

Discussion

The important findings of the present study can be summarized as follows: adenosine A1 receptor agonist CCPA is effective in decreasing arrhythmias induced by reperfusion. The timing of the administration of CCPA is found to be crucially important in decreasing the arrhythmia. Adenosine A1 receptor antagonist DPCPX was found to block the antiarrhythmic effect of CCPA, indicating that adenosine's effectiveness depends on the stimulation of the A1 receptors.

Among these findings, the time dependence of the effect is the most important and the novel observation. No comparable study that focused on the time dependent effect of adenosine was found in the literature using an experimental protocol similar to the one in the present study. Although the time dependence cannot be explained by the results of the present study, we can make some suggestions about its mechanism. It is well known that endogenous adenosine is released during the ischemic period. Since the adenosine molecule has a short lifespan, the decrease in the endogenous adenosine is replenished by the exogenous adenosine and the level of adenosine is maintained. Larger doses given before or during ligation lead to death of animals due to cardiac arrest. That is why CCPA given during ligation in a dose of 5 μg/kg may be effective in decreasing reperfusion induced arrhythmia. It may also be suggested that the effectiveness of adenosine A1 receptor agonist to decrease reperfusion induced arrhythmia given during ligation period may be related to the fact that adenosine might have effects also on non-myocardial cells. In the reperfusion process there might be no endogenous release of adenosine and exogenous adenosine is found to be non-effective, probably due to the below threshold amount. The exact mechanism for the importance of the time dependent effect of adenosine needs further study.

In the present study, adenosine A1 receptor agonist decreased the blood pressure and induced bradycardia; similar results were already observed by Shen et al. and Belloni et al. (17,18). CCPA given at the 2nd minute of ligation decreased the duration of the total arrhythmia and ventricular tachycardia with respect to the control animals. Blockage of adenosine A1 receptor prevented this protective effect.

We found that adenosine CCPA was effective in decreasing arrhythmias induced by reperfusion. Canyon et al. (15) reported that adenosine A1 agonist given at the ligation period by infusion did not decrease arrhythmia in reperfusion. However, when it was given in combination with lidocain, it was found to be effective in decreasing the ventricular arrhythmia. Wainright and Parratt (12) found that pretreatment of adenosine A1 agonist R-PIA before ligation decreased ischemia induced arrhythmia. The left ventricular infusion of adenosine reduced the incidence of ventricular fibrillation (13).

Although selective adenosine A1 receptor blocker DPCPX alone did not affect ischemia or reperfusion induced arrhythmia, it was found to suppress the antiarrhythmic effect produced by CCPA applied during the ligation period. The underlying mechanism in the antiarrhythmic effect of adenosine, especially given during the ligation period, was the subject of many studies. These studies pointed to the important relation between the adenosine A1 receptor activation and the regulation of K (ATP) channel opening (19,20). The antiarrhythmic effect produced by adenosine is similar to the effect of ATP dependent potassium channel opener (17). Both agents have antiadrenergic effects and cause bradycardia and even cardiac arrest (21). Some researchers suggest that openers decrease infarct size and arrhythmia (20,22), but others report opposite results (23,24). The same is true for ATP dependent potassium channel blocker (25,26). If the adenosine A1 receptor activation leads to the opening of the K (ATP) channel, blockage of the adenosine A1 receptor could be expected to keep the channel closed. In the present study, blockage of adenosine A1 receptor was found not to increase the reperfusion induced arrhythmia, but it reversed the antiarrhythmic effect of adenosine. Lee et al. (27) showed that DPCPX enhanced arrhythmia but adenosine A1 receptor agonist BN-063 given before ligation decreased arrhythmia after 30 min of coronary ligation. The effectiveness of DPCPX in that study may depend on a higher dose of DPCPX. During the present study DPCPX was used in a dose of 5 μg/kg, but previously Lee et al. (27) used DPCPX in a 0.5 mg/kg dose.

In summary of the findings of the present study, the effect of adenosine agonist CCPA on the ischemia/reperfusion induced arrhythmia depends on the time and dose of its administration. Adenosine agonist given in a bolus injection just following coronary ligation in rats is effective in decreasing reperfusion induced arrhythmia.

Acknowledgment

We thank Assoc. Prof. Dr. Resul Eryiğit from Faculty of Arts and Sciences in Abant İzzet Baysal University for his critical reading of the manuscript.

References

1. Overholt ED, Rheuban KS, Gutgesell HP, Lerman BB, Dimarco JP. Usefulness of adenosine for arrhythmias in infants and children. Am J Cardiol 1988; 61: 336-340.
2. Wilbur SL., Marchlinski FE. Adenosine as an antiarrhythmic agent. Am J Cardiol 1997; 79: 30-37.
3. Noji T, Karasawa A, Kusaka H. Adenosine uptake inhibitors. Eur J Pharmacol 2004; 495: 1-16.
4. Tan HL, Spekhorst HHM, Peters RJG, Wilde AAM. Adenosine induced ventricular arrhythmias in the emergency room. PACE 2001; 24: 450-455.
5. Obata T. Adenosine production and its interaction with protection of ischemic and reperfusion injury of the myocardium. Life Sci 2002; 71: 2083-2103.
6. Mubagwa K, Flameng W. Adenosine, adenosine receptors and myocardial protection: An updated overview. Cardiovasc Res 2001; 52: 25-39.
7. De Jonge RD, Out M, Maas WJ, De Jong JW. Preconditioning of rat hearts by adenosine A1 or A3 receptor activation. Eur J Pharmacol 2002; 441: 165-172.

8. Miura T, Ishimoto R, Sakamoto J, Tsuchida A, Suzuki K, Ogawa T et al. Suppression of reperfusion arrhythmia by ischemic preconditioning in the rat: Is it mediated by the adenosine receptor, prostoglandin, or bradykinin receptor? Basic Res Cardiol 1995; 90: 240-246.

9. Vegh A, Papp JG, Parratt JR. Pronounced antiarrhythmic effects of preconditioning in anaesthetized dogs: is adenosine involved? J Mol Cell Cardiol 1995; 27: 349-356.

10. Ganote CE, Armstrong SC. Adenosine and preconditioning in the rat heart. Cardiovasc Res 2000; 45: 134-140.

11. Tissier R, Souktani R, Parent de Curzon O, Lellouche N, Henry P, Giudicelli JF et al. Pharmacological delayed preconditioning against ischemia-induced ventricular arrhythmias: Effect of an adenosine A1-receptor agonist. Br J Pharmacol 2001; 134: 1532-1538.

12. Wainwright CL, Parratt JR. Effects of R-PIA, a selective A1 adenosine agonist, on haemodynamics and ischaemic arrhythmias in pigs. Cardiovasc Res 1993; 27: 84-89.

13. Wainwright CL, Parratt JR. An antiarrhythmic effect of adenosine during myocardial ischaemia and reperfusion. Eur J Pharmacol 1988; 145: 183-194.

14. Pelleg A, Kutalek SP. Adenosine in the mammalian heart: nothing to get excited about. TIPS 1997; 18: 236-238.

15. Canyon SJ, Dobson GP. Pretreatment with an adenosine A1 receptor agonist and lidocaine: A possible alternative to myocardial ischemic preconditioning. J Thorac Cardiovasc Surg 2005; 130: 371-377.

16. Walker MJA, Curtis MJ, Hearse DJ, Campbell RWF, Janse MJ, Yellon DM et al. The Lambeth Conventions: guidelines for the study of arrhythmias in ischemia, infarction, and reperfusion. Cardiovasc Res 1988; 22: 447-455.

17. Shen FM, Zhu GM, Miao CY, Guan YF, Su DF. ATP-sensitive potassium channels are involved in adenosine-induced reduction of blood pressure variability in spontaneously hypertensive rats. J Cardiovasc Pharmacol 2004; 44: 87-92.

18. Belloni FL, Wang J, Hintze TH. Adenosine causes bradycardia in pacing-induced cardiac failure. Circulation 1992; 85: 1118-24.

19. Baxter GF. Role of adenosine in delayed preconditioning of myocardium. Cardiovasc Res 2002; 55: 483-494.

20. Grover GJ. Protective effects of ATP-sensitive potassium-channel openers in experimental myocardial ischemia. J Cardiovasc Pharmacol 1994; 24: S18-S27.

21. Cohen NM, Wise RM, Wechsler AS, Damiano RJ Jr. Elective cardiac arrest with a hyperpolarizing adenosine triphosphate-sensitive potassium channel opener. A novel form of myocardial protection? J Thorac Cardiovasc Surg 1993; 106: 317-28.

22. Baczko I, Lepran I, Papp J Gy. K_{ATP} channel modulators increase survival rate during coronary occlusion-reperfusion in anaesthtized rats. Eur J Pharmacol 1997; 324: 77-83.

23. Black SC, Lucchesi BR. Potassium channel openers are likely to be proarrhythmic in the diseased human heart. Cardiovasc Res 1994; 28: 923.

24. Kaiser J, Englert HC, Kurjat M, Linz W. Profibrillatory effect of pinacidil and its antagonism by low concentrations of glibenclamide in isolated guinea pig hearts. Naunyn-Schmiedeberg's Arch Pharmacol 1994; 349: R46.

25. Bozdoğan Ö, Lepran I, Papp JGy. The effect of ATP-dependent potassium channel blocker, Glimeprid, on the arrhythmias observed following ischemia and reperfusion in anesthesized Rats. Tr J of Vet Anim Sci 1998; 22: 247-254.

26. Bozdogan Ö, Gonca E, Nebigil M, Tiryaki SE. Effect of Thimerosal on arrhythmia induced by coronary ligation: the involvement of ATP-dependent potassium channels. Int Heart J 2005; 46: 711-722.

27. Lee YM, Chern JW, Yen MH. Antiarrhythmic effects of BN-063, a newly synthesized adenosine A1 agonist, on myocardial ischemia in rats. Br J Pharmacol 1994; 112: 1031-1036.