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Electrophysiologic Effects of Adenosine Triphosphate and Adenosine on the Mammalian Heart: Clinical and Experimental Aspects

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Adenosine triphosphate (ATP) and adenosine have strong negative chronotropic and dromotropic effects on the mammalian heart. The sensitivity of the sinus node and the atrioventricular node to ATP and adenosine manifests pronounced variability among species. For more than three decades, ATP has been used routinely in Europe in the acute therapy of paroxysmal supraventricular tachycardia. Preliminary clinical trials with adenosine in the United States suggest that this compound may have a similar therapeutic value. The exact mechanisms of action of ATP and adenosine on the mammalian heart are still not fully known. However, the vast clinical experience indicates that ATP, and probably also adenosine, can be safely and repetitively used in the acute therapy of paroxysmal supraventricular tachycardia.

More than 50 years ago, Drury and Szent-Gyorgyi (1) found that "simple extracts of heart muscle and other tissues, when injected intravenously into the whole animal, disturbed the cardiac rhythm in a constant and definite manner, and the substance or substances involved were dealt with quickly and efficiently by the whole animal so that the pre-injection state was completely restored." They elegantly studied this original observation and concluded that the negative chronotropic and dromotropic effects observed in several mammalian species were caused by exogenous adenine compounds (1,2). Their original findings have since been confirmed in numerous studies. Transient negative chronotropic and dromotropic effects of adenosine triphosphate (ATP) and adenosine were demonstrated in human beings as well as in animal models (3–26).

The electrophysiologic effects of ATP led to its wide use in Europe as a potent antiarrhythmic agent for the management of paroxysmal supraventricular tachycardia (27–33). Preliminary studies (26) in the United States have indicated that adenosine is similarly effective in the treatment of this tachycardia. The chronotropic and dromotropic effects of adenosine were recently reviewed by Belardinelli et al. (34).

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This review summarizes clinical and experimental data on the electrophysiologic effects of ATP and adenosine and discusses possible mechanisms of action of these compounds.

Basic Studies

Since the early report of Drury and Szent-Gyorgyi (1), the electrophysiologic effects of ATP, adenosine and related compounds on the mammalian heart have been extensively studied. The major finding was that both compounds exert transient negative chronotropic (Fig. 1) and dromotropic effects on the sinoatrial (SA) and atrioventricular (AV) node, respectively. However, the magnitude of these effects differed in various species and experimental models. Moreover, contradictory results were obtained when the influence of either atropine or vagotomy on the effects of ATP was studied. Therefore, these results are reviewed in chronologic order according to the species studied (Table 1).

Guinea pig. Drury and Szent-Gyorgyi (1) found that in the guinea pig, the administration of 0.5 g extract of the bullock's heart muscle in the jugular vein caused a slight degree of slowing of sinus rhythm but had a more pronounced effect on the AV node, that is, causing transient complete block. These effects were unaltered by the administration of atropine sulfate. The active substance in the heart extract was identified as adenylic acid. Adenosine obtained from yeast nucleic acid had similar effects (1).

Similar depressant effects of ATP and adenosine, predominant in the AV node, were reported by Wayne et al. (6). These effects of both ATP and adenosine were not influenced by cervical vagotomy. In 1966, Stafford (11)

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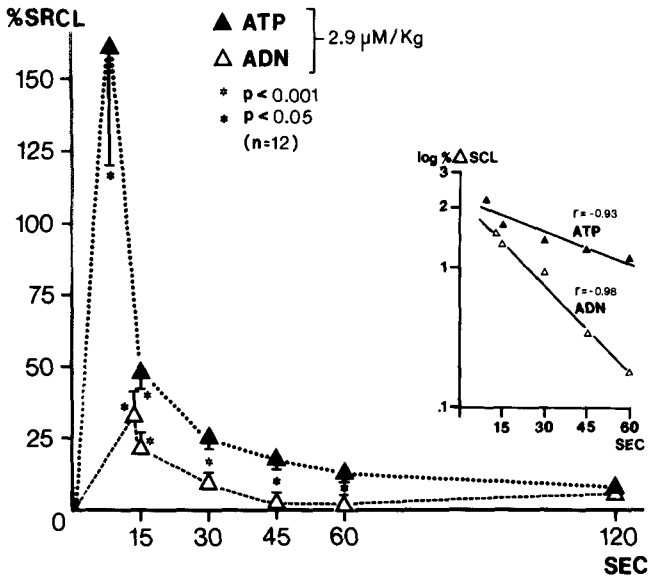

Figure 1. Transient negative chronotropic action of ATP and adenosine (ADN) (2.90 μM/kg administered into the right atrium in less than 1 second; n = 12) in the intact canine heart, expressed as the percent increase in sinus rhythm cycle length (%SRCL ± SEM). Maximal effects of ATP and adenosine occur 9.5 ± 1.2 and 13.1 ± 0.6 seconds ($p < 0.01$) after their administration, respectively. These effects decrease in an exponential manner, and no significant chronotropic changes are present 60 seconds after the administration of ATP and adenosine. The maximal effect of ATP is significantly more pronounced than that of adenosine ($p < 0.05$). The **inset** shows that the disappearance of the effects of ATP and adenosine closely follows the mathematical expression for the first order kinetics ($[A] = [A]_0 \cdot e^{-kt}$) because the semilogarithmic plot of the mean effect of ATP and adenosine versus time is nearly linear with the correlation coefficient of −0.93 and −0.98 respectively.

showed that the heart block caused by injection of 25 μg adenosine in the guinea pig left atrium was transiently potentiated by a single dose of dipyridamole (100 to 800 μg/kg). The similar effects of ATP were also potentiated by dipyridamole. Schondorf et al. (12) found that in the isolated guinea pig heart, adenosine caused pronounced sinus bradycardia and an increase in coronary blood flow.

More recently, Belardinelli et al. (17) showed a dose-dependent prolongation of AV conduction and AV block caused by adenosine in the perfused guinea pig heart. Conduction delay was confined to the AH interval, implicating adenosine action on the AV node. Similar AV conduction delay and block were observed under hypoxic conditions. These effects were not influenced by atropine, but were significantly attenuated by aminophylline. On the basis of these results, Belardinelli et al. (17) suggested that endogenously released adenosine may explain, in part, the AV conduction disturbances associated with acute myocardial hypoxia. This hypothesis is in concert with previous studies of Szentmiklosi et al. (35,36) in which the effects of adenosine on transmembrane potential and myocardial contractility were compared with those of hypoxia in guinea pig left atrial preparations. It was concluded in these studies that in acute myocardial hypoxia, the increased level of adenosine might contribute to the functional impairment of the atrial myocardium (35,36). In another study, Belardinelli et al. (37) compared the effects of purines on the AV node of the perfused guinea pig heart. In contrast to Wayne et al. (6), they found that adenosine was more potent than ATP and concluded that the ATP-induced prolongation of AH interval and AV block is a consequence of its rapid degradation to adenosine.

Rabbit. Drury and Szent-Gyorgyi (1) reported that doses up to 100 mg of adenosine administered intravenously to unanesthetized rabbit produced a very transient bradycardia. Almost 20 years later, Emmelin and Feldberg (5) found that injection of ATP into the left auricle of the rabbit caused pronounced bradycardia that was not prevented by either vagotomy or atropine. The magnitude of this response was dose-dependent, but with repeated injections the slowing became gradually less pronounced. More recently, Belardinelli et al. (17) found that adenosine had a similar effect on perfused guinea pig and rabbit hearts; however, the rabbit heart was less sensitive to adenosine.

Cat. In 1948, Emmelin and Feldberg (5) reported that in cats anesthetized with chloralose, 0.2 to 0.4 mg ATP injected into either the left auricle or left coronary artery produced pronounced bradycardia. This negative chronotropic effect was abolished by vagotomy. The slowing of heart rate was often less pronounced when similar doses of ATP were injected into the ascending aorta.

Wayne et al. (6) also studied the effects of ATP and adenosine in the cat. They reported that the administration of 0.3 to 1.0 mg/kg magnesium adenosine triphosphate (MgATP) resulted in short-lasting sinus bradycardia and complete AV block. These affects on the SA and AV nodes were not reproduced by equimolar amounts of adenosine. A section of the vagi, however, equated the effects of ATP and adenosine.

Dog. In 1929, Drury and Szent-Gyorgyi (1) described the effects of adenosine (up to 50 mg) injected into the femoral vein of dogs anesthetized with morphine and chloralose. The sinus rhythm was consistently slowed by the injection in a dose-dependent manner. The onset of the bradycardia was 10 to 15 seconds after the injection, and it gradually disappeared. Vagal block with atropine did not modify the effects of adenosine on the heart rate. By means of atrial pacing, Drury and Szent-Gyorgyi (1) found that adenosine consistently shortened the atrial absolute refractory period. In the presence of adenosine, atrial flutter and fibrillation could be readily induced by atrial pacing. In contrast to its pronounced effects on the atria, adenosine (up to 100 mg) did not affect the electrophysiologic characteristics of the ventricle.

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Table 1. Negative Chronotropic and Dromotropic Effects of ATP and Adenosine in the Mammalian Heart

Drug	Dose	Administration	Effect on SAN	Effect on AVN	Vagal Involvement	Reference (first author)
			Guinea Pig			
Adenyl-cyclic	0.5 g	Jugular vein	+	+ + +	–	Drury (1)
MgATP	0.5 to 1 mg/kg	Jugular vein	+	+ + +	–	Wayne (6)
Adenosine	*	Jugular vein	+	+ + +	–	Wayne (6)
Adenosine	25 μg	Left atrium	···	+ + +	···	Stafford (11)
ATP	**	Left atrium	···	+ + +	···	Stafford (11)
Adenosine	10^{-4} to $10^{-7}M$	Isolated heart	···	+ + +	–	Belardinelli (17)
Adenosine	$7 \times 10^{-6}M$, $2 \times 10^{-5}M$	Isolated heart	···	+ + +	···	Belardinelli (37)
ATP	$7 \times 10^{-6}M$, $2 \times 10^{-5}M$	Isolated heart	···	+	···	Belardinelli (37)
			Rabbit			
Adenosine	100 mg	Femoral vein	+ + +	–	···	Drury (1)
ATP	0.05 mg	Left auricle	+ + +	–	–	Emmelin (5)
Adenosine	10^{-7} to $10^{-4}M$	Isolated heart	···	+ +	–	Belardinelli (17)
			Cat			
ATP	0.2 to 0.4 mg	Left atrium	+ + +	–	+	Emmelin (5)
MgATP	0.3 to 1 mg/kg	Jugular vein	+ + +	+ +	+	Wayne (6)
Adenosine	*	Jugular vein	+	–	···	Wayne (6)
			Dog			
Adenosine	50 mg	Femoral	+ + +	–	–	Drury (1)
ATP	0.2 mg	Left auricle	+ + +	–	+	Emmelin (5)
Adenosine	0.1 to 2 mg/kg	Jugular vein	+ + +	···	–	Angelakos (8)
ATP, adenosine	1 to 1,000 μg	SA nodal artery	+ + +	–	–	James (9)
ATP	100 g-10 mg	AV nodal artery	···	+ + +	–	Urthaler (14)
Adenosine	100 g-10 mg	AV nodal artery	···	+	···	Urthaler (14)
Adenosine	0.3 to 10 μg	SA nodal artery	+ + +	···	···	Chiba (15)
Adenosine	10 to 1,000 μg	AV nodal artery	···	+ + +	···	Belardinelli (18)
ATP	1.6 mg/kg	Right atrium	+ + +	+ + +	+	Pelleg (25)
Adenosine	2 mg/kg	Femoral vein	···	+	–	Munoz (23)
			Human Being			
MgATP	15 to 40 mg	IV	+ + +	+ + +	+	Wayne (6)
ATP	20 mg	IV/right atrium	+ + +	+ + +	–	Leclercq (16)
ATP	Variable	IV	···	+ + +	–	Lechat (20,21)
Adenosine	190 ± 88μg/kg	IV	+	+ +	–	DiMarco (26)

ATP = adenosine triphosphate; AVN = atrioventricular node; IV = intravenous; SAN = sinoatrial node; * = equimolar dose of the previously administered ATP and adenosine (**); +, + + and + + + = weak, moderate and strong effect, respectively; – no effect; ··· indicates unavailable data.

The effects of ATP in dogs were studied by Emmelin and Feldberg (5). They found that injection of ATP (0.2 mg) into the left auricle or the base of the aorta caused pronounced slowing of the heart that could be prevented by either vagotomy or atropine. In contrast, the latter interventions did not interfere with the cardiovascular actions of adenosine (8).

Using an open chest model with direct perfusion of the SA nodal artery, James (9) studied the effects of ATP and related compounds on the canine heart. Administration of equimolar amounts of ATP and adenosine resulted in an immediate, transient negative chronotropic effect of equal magnitude. The magnitude and the duration of sinus bradycardia were linearly dependent on the injected dose of ATP and adenosine. The negative chronotropic effect of ATP and adenosine was not altered by intravenous administration of atropine. Using a similar method, Urthaler and James (14) evaluated the effects of ATP and adenosine on the canine AV node. They found that the administration of ATP resulted in various degrees of transient AV block and that

adenosine did not produce any direct dromotropic effect. However, a similar negative chronotropic effect on AV junctional escape rhythm was obtained with ATP and adenosine in this model. Neither bilateral vagotomy nor the administration of atropine altered the response to ATP. Chiba and Hashimoto (13) used a similar preparation of selective perfusion of the canine SA and AV nodal arteries to compare the effects of acetylcholine and adenosine. Adenosine induced almost the same degree of sinus bradycardia as acetylcholine. In contrast, adenosine had a much smaller effect on the AV node such that only high doses produced a low degree AV block. In the isolated canine right atrium perfused with blood through the SA nodal artery, Chiba (15) found that 0.3 to 10 μg adenosine caused a negative chronotropic and inotropic effect. These effects were potentiated by dipyridamole, an inhibitor of nucleoside transport (38,39).

More recently, Belardinelli et al. (18) did find a dose-dependent, transient increase in AV conduction and AV block after the rapid administration of 10 to 100 μg adenosine into the AV nodal artery in an open chest canine model. A dose of 1 mg of adenosine caused a transient second degree AV block. Dipyridamole potentiated the negative dromotropic effects of adenosine, whereas aminophylline, a competitive antagonist of adenosine (40,41), attenuated them.

In a closed chest canine model, Pelleg et al. (25) found that both ATP and adenosine (1.6 mg/kg) administered into the right atrium exerted strong transient negative chronotropic and dromotropic effects on the SA and AV node, respectively. The effects of ATP, however, were more pronounced than those of adenosine. Either atropine (0.2 mg/kg) or bilateral cervical vagotomy after propranolol administration (0.5 mg/kg) markedly attenuated the effects of ATP but not of adenosine. In the presence of propranolol and vagotomy, when the action of ATP and adenosine were practically identical, aminophylline and dipyridamole attenuated and enhanced, respectively, the effects of ATP and adenosine in a similar manner (Pelleg et al., unpublished observations). Similar results with regard to the differential potencies of ATP and adenosine and the involvement of the vagus in the mechanism of action of ATP were reported by Munoz et al. (23).

In summary, the potencies of the chronotropic and dromotropic effects of ATP and adenosine show pronounced variability among species. Whereas in guinea pigs the AV node is more sensitive to ATP and adenosine than is the sinus node (1,6) the opposite is true in dogs, cats and rabbits. Adenosine is more potent than ATP in the guinea pig (37), less potent in the dog and cat (6,23,25) and equipotent in the rabbit (17). The mechanism of action of ATP and adenosine seems also to be different. Vagal involvement was demonstrated in the action of ATP in several species (5,6,23,25), but it was not found in the action of adenosine.

Hemodynamic effects. In addition to their electrophysiologic effects, ATP and adenosine have pronounced effects on cardiovascular hemodynamics. Both compounds produce a dose-dependent coronary and peripheral vasodilation that is more pronounced for ATP than for adenosine (42,43). This action results in a significant decrease in arterial blood pressure that reaches a maximum in 15 to 30 seconds. Blood pressure fully recovers to control values within 2 to 3 minutes (1,4,5,8). The decrease in blood pressure is not affected by vagotomy or muscarinic cholinergic blockade. The peripheral vasodilation results in baroreflex tachycardia that is suppressed by beta-adrenergic receptor blockade (44). In cats, the decrease in blood pressure was attributed, in part, to transient obstruction of pulmonary circulation (5).

The negative chronotropic effects of ATP and adenosine tend to obscure their inotropic effects. Depending on the species and the cardiac tissue studied, negative or positive inotropic effects, or both, were observed (14,45).

Human Studies

Clinical and Electrophysiologic Effects

Effects on the normal conducting system. Despite the wide clinical use of ATP in the therapy of supraventricular tachycardia, only a few studies evaluated its electrophysiologic effects on the normal conducting system of the human heart. Wayne et al. (6) observed dose-related negative chronotropic and dromotropic effects of MgATP in the human heart. Small doses of 5 to 15 mg, administered intravenously as a bolus, produced sinus tachycardia preceded by a short period of sinus slowing. Larger doses of MgATP (15 to 30 mg) resulted in pronounced sinus bradycardia and a first or a second degree AV block. A maximal dose of 30 to 40 mg produced similar changes but of greater intensity. Using the highest dose, ventricular standstill was observed in some patients. Using equimolar doses of MgATP and adenosine in two patients, Wayne et al. found that adenosine had effects similar to those of ATP but was less potent. In five patients, atropine diminished the negative chronotropic and dromotropic effects of MgATP. Leclercq and Coumel (16) studied the effects of ATP (20 mg bolus injection) administered during sinus rhythm into a peripheral vein or the right atrium. They observed one or several of the following: sinus bradycardia, AV block and secondary sinus tachycardia. The latter was most frequently noted.

Lechat et al. (20,21) compared the effects of atropine and aminophylline on the transient complete AV nodal block induced by ATP during atrial pacing. The conduction disturbances caused by ATP were not affected by administration of 0.03 mg/kg atropine, but were prevented by aminophylline (2 to 5 mg/kg), a competitive antagonist of adenosine (22,46,47); similar results were obtained by Favale et al. (19,24).

More recently, DiMarco et al. (26) administered an intravenous bolus of adenosine to 17 patients during electrophysiologic studies. A mean dose of 190 ± 88 μg/kg given to 15 patients during sinus rhythm, produced in all a greater than 50% increase in sinus cycle length. In 17 patients, a mean dose of 179 ± 88 μg/kg of adenosine prolonged AV nodal conduction, leading to complete AV nodal block. These changes occurred 10 to 20 seconds after the injection and lasted less than 10 seconds. Atropine (0.02 to 0.03 mg/kg) did not alter these effects of adenosine.

In summary, these studies showed that both ATP and adenosine exert strong transient chronotropic and dromotropic effects on the SA and AV node, respectively. The involvement of the vagus in the action of adenosine or ATP was ruled out in all studies with the exception of one (6). Whether this discrepancy could be explained by the fact that in the latter study the magnesium salt of ATP was used is undetermined. The fact that aminophylline and not atropine attenuated the effects of ATP in human beings (20,24) suggests a direct action of ATP or its metabolites, or both.

Effects on tachyarrhythmias: clinical studies (Table 2). The earliest report that we could find on the effects of ATP in paroxysmal supraventricular tachycardia is by Somlo (27) in 1955. He reported that more than 200 episodes of the tachycardia were terminated by rapid intravenous administration of 20 mg of ATP. Cardiac standstill, lasting 2 to 4 seconds, was commonly seen 18 to 20 seconds after the administration of the drug. The asystole was sometimes interrupted by either atrial or ventricular extrasystoles originating from various foci. Gradual recovery to normal sinus rhythm was observed, and after a few complexes the electrocardiogram had a normal configuration.

Komor and Garas (28) reported on 300 administrations of ATP in 52 patients with paroxysmal supraventricular tachycardia (including one patient who received ATP 183 times over a period of 4 years). In 250 episodes, ATP promptly terminated the tachycardia. In most of these cases, a dose of 10 to 40 mg of ATP was found effective; however, doses of up to 70 mg were administered without any harmful effects.

The effects of ATP on various types of tachycardia were extensively studied in France. Latour et al. (29) administered 10 to 20 mg of ATP in 39 patients having 51 episodes of tachycardia (43 episodes of AV junctional tachycardia, 7 of various atrial arrhythmias and 1 of ventricular tachycardia). ATP did not affect the ventricular tachycardia but terminated 42 of 43 episodes of AV junctional tachycardia and transiently slowed the ventricular rate of all atrial tachyarrhythmias.

Motté et al. (30) administered intravenously 20 mg of ATP during 49 episodes of tachycardia in 36 patients. Conversion to sinus rhythm was obtained within 30 seconds in 40 of 41 episodes of AV junctional tachycardia. The administration of ATP in eight patients during episodes of tachycardia of undetermined origin with wide QRS configuration gave the following results: in five cases, ventricular rate transiently slowed, indicating the presence of atrial flutter; in one case, termination of the tachycardia suggested the involvement of AV reentry; in one case, transient ventriculoatrial block without any change in the ventricular rate suggested that the tachycardia had a ventricular origin and in one case, no change in the rate of the tachycardia was observed. Later studies in this patient indicated that the tachycardia was atrial flutter with conduction through an accessory pathway.

In summary, these clinical studies demonstrated that ATP is a highly effective agent for the acute therapy of paroxysmal supraventricular tachycardia. In addition, ATP can

Table 2. Effects of ATP and Adenosine in Various Tachyarrhythmias

Drug	Dose	Arrhythmia	No. of Patients	No. of Episodes	Conversion	Side Effects	Reference (first author)
ATP	20 to 30 mg	PSVT	—	214	—	Minor	Somlo (27)
ATP	10 to 70 mg	PSVT	52	300	—	Minor	Komor (28)
ATP	10 to 20 mg	PSVT	39	43	42 (98%)	Convulsions (1)	Latour (29)
	10 to 20 mg	AT		7	0	Asthma (1)	
	10 to 20 mg	VT		1	0		
ATP	20 mg	PSVT	36	42	41 (98%)	Minor	Motté (30)
	20 mg	AT		5	0	Syncopal	
	20 mg	VT		1	0	cardiac pause (2)	
	20 mg	AT/WPW		1	0		
ATP	3 to 15 mg	PSVT	—	36	32 (89%)	Minor	Greco* (32)
ATP	20 mg	PSVT	18	18	17 (94%)	Minor	Belhassen (33)
Adenosine	83 ± 35 μg/kg	PSVT	5	32	32 (100%)	Minor	DiMarco (26)
	83 ± 35 μg/kg	AT	1	—	0		
ATP	—	PSVT	10	10	10 (100%)	Minor	Tajima (50)
	—	AT	2	2	1		

*Infants and children; AT = atrial tachycardia; PSVT = paroxysmal supraventricular tachycardia; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome; — = unavailable data.

cause transient slowing of the ventricular rate during atrial tachyarrhythmias, but has no effect on ventricular tachycardia.

Effects on tachyarrhythmias and pre-excitation: electrophysiologic studies. In contrast to the wide clinical use of ATP in the management of supraventricular tachycardia, only a few electrophysiologic studies were performed in patients with tachyarrhythmias and pre-excitation. Perrot and Faivre (48,49) administered intravenously 20 to 40 mg of ATP to patients with manifest or concealed pre-excitation and to patients with a short PR interval and normal QRS complex. Whenever pronounced alteration in antegrade nodal conduction was observed, ventricular pacing was initiated. Increase in the degree of pre-excitation was seen in 15 of the 22 patients with Wolff-Parkinson-White syndrome. In the remaining seven patients, administration of ATP completely abolished the pre-excitation pattern. The latter group of patients had either prolonged refractory period of the accessory pathway or associated James and Mahaim fibers. The administration of ATP during ventricular pacing did not alter retrograde conduction through the accessory pathway in 17 patients. However, in the remaining five patients, retrograde conduction was prolonged or completely abolished. In 10 patients with concealed accessory pathways, antegrade pre-excitation did not appear after the administration of ATP. ATP did not alter retrograde conduction through the accessory pathway in 7 of these 10 patients but depressed it in 3 patients. In the 16 patients with a short PR interval and normal QRS complex, ATP depressed retrograde conduction in 11, but did not affect it in 5 patients. On the basis of these results, Perrot and Faivre (48,49) concluded that ATP depressed conduction in the AV node and in those accessory pathways that either had a prolonged refractory period or involved the AV node.

More recently, Belhassen et al. (33) administered intravenously 20 mg of ATP to 18 patients with AV reentrant tachycardia, during both tachycardia and ventricular pacing. ATP terminated the tachycardia within 16 seconds in eight of nine patients with AV nodal reentry and in all nine patients with an accessory pathway (Fig. 2). Termination of the tachycardia in these two groups of patients was due to a block in the antegrade slow pathway and in the AV node, respectively. In one patient with AV nodal reentry, ATP slowed the rate of the tachycardia by delaying conduction in the slow antegrade pathway. The administration of ATP during ventricular pacing resulted in transient complete ventriculoatrial block or slight prolongation of the retrograde conduction time in five of the nine patients with AV nodal reentry, but it did not alter retrograde conduction in the remaining four patients. In all patients with an accessory pathway, retrograde conduction through the pathway was not affected by ATP; similar results were reported by Tajima et al. (50).

The discrepancy between the results of Perrot and Faivre (48,49) and those of Belhassen et al. (33) may be explained by the following: 1) In the former study higher doses of ATP were administered; 2) the accessory pathways in patients of the latter study had shorter refractory periods than those of patients in the former study; 3) in the latter study, no evidence for the presence of James and Mahaim fibers was found; and 4) the ATP-sensitive accessory pathways of the former study might have included aberrant AV nodal tissue.

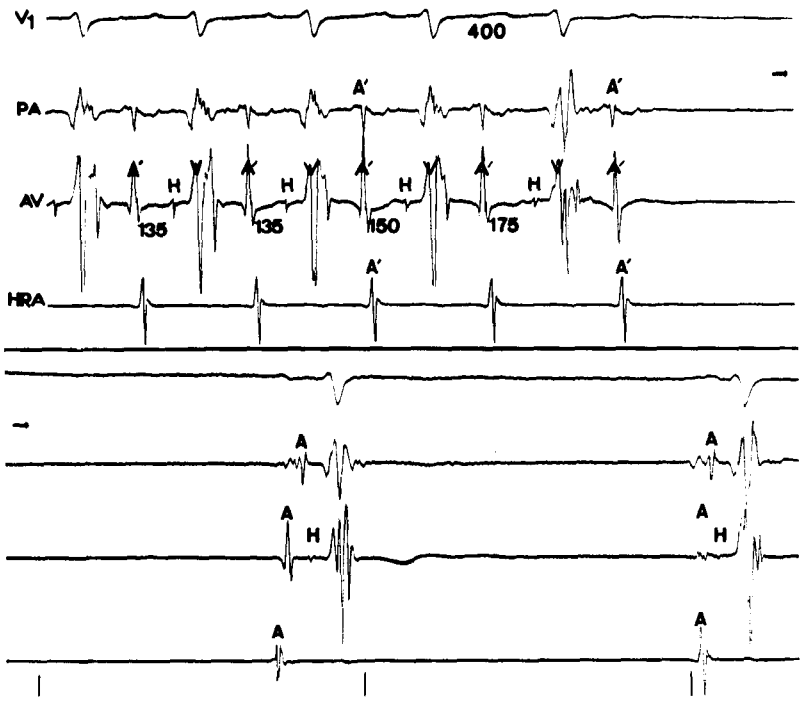


Figure 2. The effects of ATP (20 mg administered intravenously in 1 second) during atrioventricular reentrant tachycardia in a patient with a concealed left lateral accessory pathway. **Tracings from top to bottom** are: electrocardiographic lead V_1, pulmonary artery trunk electrogram (PA), AV junctional electrogram (AV) and high right atrial electrogram (HRA). Termination of the tachycardia occurs 9 seconds after the drug administration owing to AV nodal block after a progressive increase in A'H interval. No significant change in accessory pathway conduction is noted. Sinus bradycardia at a cycle length of 1,300 ms is subsequently present for 5 seconds. A and A' denote antegrade and retrograde atrial activity, respectively; H = His bundle deflection; V = ventricular activity. (Reprinted from Belhassen B, et al. [33] with the permission of the American Heart Association, Inc.)

In a preliminary report, DiMarco et al. (26) described the effects of adenosine on AV reentrant tachycardia involving AV nodal reentry in two patients and retrograde accessory pathways in three patients. Adenosine (83 ± 35 μg/kg) terminated all episodes of induced tachycardia within 10 to 20 seconds after prolongation of AV nodal conduction time (Fig. 3). DiMarco and coworkers noted that the dose of adenosine required to terminate the tachycardias was equal to or less than the dose required to produce either sinus bradycardia or AV block during sinus rhythm. In five patients with supraventricular tachycardia, adenosine terminated the tachycardia in the presence of atropine. In two patients, however, a higher dose of adenosine was required to terminate the arrhythmia. In patients with Wolff-Parkinson-White syndrome, DiMarco et al. did not find any effect of adenosine on the antegrade conduction in the accessory pathways.

In summary, electrophysiologic studies of ATP and adenosine administration on supraventricular tachycardia in human beings confirm their strong negative dromotropic effects on the AV node. However, both agents only affect those accessory pathways that have a prolonged refractory period or involve the AV node.

ATP compared with other antiarrhythmic agents. Greco et al. (32) compared the efficacy of digitalis, ATP and verapamil in the treatment of paroxysmal supraventricular tachycardia in infants and children. They found that ATP was as effective as verapamil in terminating the tachycardia (90% success rate) and more effective than digitalis. In their study, severe adverse effects were noted in two patients after the administration of verapamil. In contrast, frequent but benign side effects were observed after the administration of ATP.

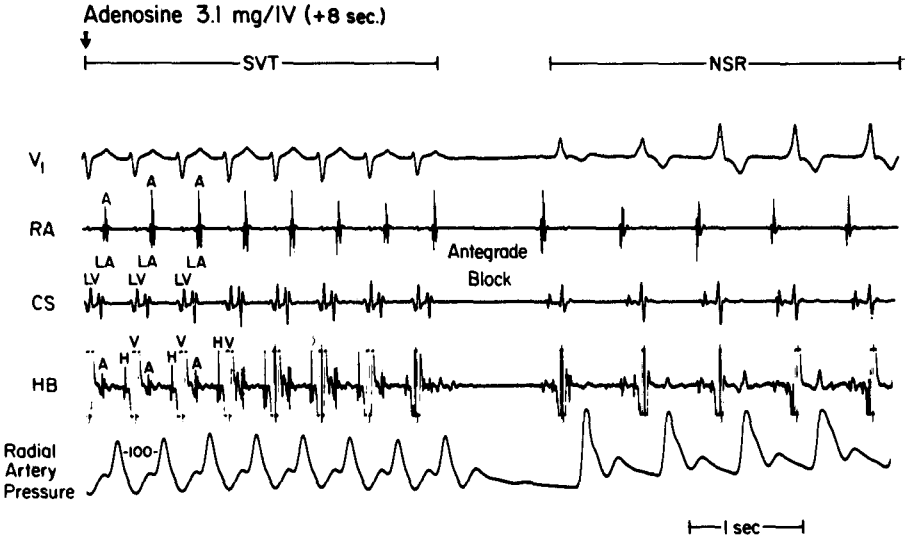
Preliminary results in adult patients (Belhassen et al., unpublished data) showed that administration of ATP resulted in prompt termination of paroxysmal supraventricular tachycardia resistant to verapamil, ajmaline and digoxin.

Potency

The rate of administration has a pronounced influence on the potency of ATP. When administered slowly, ATP causes an acceleration in sinus rate (51). This is probably due to reflex response after the systemic vasodilation caused by ATP. In contrast, sinus bradycardia or depressed AV conduction, or both, is common when ATP is administered rapidly as a bolus injection.

The site of administration also influences the potency of ATP. Leclercq and Coumel (16) compared the effects of ATP administered through a peripheral vein and into the right atrium. They found that the effects of ATP, given in the latter mode, were more frequent, more intense and quicker in onset. This finding could be explained by the rapid intravascular degradation of ATP (52–54).

Figure 3. The effects of intravenous bolus administration of adenosine (75 μg/kg) during atrioventricular reentrant tachycardia (SVT) in a patient with Wolff-Parkinson-White syndrome. Shown from **top to bottom** are: electrocardiographic lead V_1, intracardiac recordings of the right atrium (RA), coronary sinus (CS) and His bundle region (HB) as well as the recording of the radial artery pressure. About 11 seconds after the administration of adenosine, conduction through the AV node is blocked and normal sinus rhythm (NSR) with various degrees of preexcitation resumes. Radial artery pressure, which has been constant at 118/66 mm Hg during tachycardia, increases to 140/82 mm Hg when sinus rhythm is restored. LA = left atrial; LV = left ventricular. (Reprinted from DiMarco et al. [26] with the permission of the authors and the American Heart Association, Inc.)



Side Effects

The administration of ATP has been frequently associated with various cardiac and noncardiac side effects. These side effects are always transient, reach a maximum within 30 seconds and, excluding rare cases, disappear completely within 2 minutes. Noncardiac symptoms frequently include malaise, hyperpnea, flushing, headache and rarely retching and vomiting (6,30,32,33,51). One case of bronchial asthma and another case of convulsions have also been reported (29).

The common cardiac side effects include sinus arrest, sinus bradycardia and various degrees of AV block. These side effects are short lasting (a few seconds), usually well tolerated and do not require any intervention. In only a few instances, a thoracic blow was required to restore normal sinus rhythm when a prolonged symptomatic cardiac pause occurred (30). Rare recurrence of arrhythmias probably caused by transient atrial and ventricular hyperexcitability after the administration of ATP have also been noted (30,33). In one of our patients with a history of coronary heart disease, chest pain occurred after the termination with ATP of paroxysmal supraventricular tachycardia. This phenomenon could be explained by the transient bradycardia after ATP administration. In other similar patients, no deleterious effects were observed even when the drug was given during tachycardia associated with anginal pain (Belhassen et al., unpublished data). Recently, Tajima et al. (50) showed that pretreatment with inosine might be useful to alleviate the uncomfortable side effects of ATP.

In the study with adenosine in human subjects (26), no adverse side effects were noted with a mean dose of 179 μg/kg. Only facial flushing occurred in 5 of 17 patients. No significant decrease in the arterial blood pressure was observed; on the contrary, blood pressure slightly increased on conversion to normal sinus rhythm (Fig. 3).

In summary, transient and almost always benign side effects occur after the administration of ATP. The severity of these side effects may be reduced by the administration of smaller doses of ATP. Comparative clinical studies with ATP and adenosine are needed to determine which of the two compounds is better tolerated.

Mechanism of Action of ATP and Adenosine

The exact mechanism of action of ATP and adenosine in the mammalian heart has not been fully delineated. This is due, at least in part, to the wide spectrum of hemodynamic, biochemical and neurohumoral effects of ATP and adenosine that interact with each other and might directly and indirectly influence the electrophysiologic effects of these compounds. Some of these well documented effects of ATP and adenosine are: 1) positive and negative inotropism (4,5,7,42,55–57); 2) stimulation of prostaglandin release (58); 3) coronary vasodilation (59–62); 4) reduced release of norepinephrine from neural endings (63,64); and 5) inhibition of myocardial effects of catecholamines (65,66).

Adenosine and ATP receptors. In 1976, Burnstock (67) drew attention to the potent extracellular actions of purine nucleotides and nucleosides on excitable membranes. He later proposed (42,47) that there are two types of purinergic receptors, P_1 and P_2, different from cholinergic muscarinic receptors, which mediate the action of adenosine and ATP, respectively. The P_1 receptor is most sensitive to adenosine and is competitively blocked by methylxanthines, whereas the P_2 receptor is most sensitive to ATP. Competitive antagonists at the P_2 receptor have not been identified. In recent years, attempts have been made to further characterize P_1 receptors using the apparent order of potency of adenosine and its analogs (68). Thus, Wolff et al. (69) proposed two sites for adenosine receptors: the external and cytoplasmic surfaces of the cell membrane designated as R and P sites, respectively. The R site preferentially accepts adenosine analogs with unmodified ribose ring and the P site accepts the ribose-modified analogs. On the basis of their effects on adenylate cyclase, the former receptors were subclassified into stimulatory and inhibitory receptor, Ra and Ri (or A_2 and A_1), respectively (70,71). However, the presence of external adenosine receptors that are not functionally linked to the adenylate cyclase system has also been shown (72).

Mediation of adenosine cardiovascular effects. The question as to what type of receptor mediates a given cardiovascular effect of adenosine is still unanswered. Concerning the vasodilating and negative inotropic effects of adenosine, early studies (73–75) showed that a cell surface receptor is involved. Further work (76,77) indicated that in the guinea pig atrium the negative inotropic effect of adenosine is mediated by an A_1-receptor. However, more recent data obtained by Hughes and Stone (78) led them to conclude that the purine receptor mediating these effects should not be classified on the A_1/A_2 system. The mechanisms involved in the electrophysiologic effects of adenosine are also unclear. Evidence for the involvement of R type receptors in the negative dromotropic action of adenosine was found by Belardinelli et al. (22). The suppressing effect of adenosine on ventricular automaticity (79) was also attributed to its binding to purine receptors located in the specialized pacemaker fibers of the ventricular tissue (80). More recently, Endoh et al. (81) concluded that the negative chronotropic action of adenosine is not associated with changes of cyclase function.

Because close relations between cyclic adenosine monophosphate (cAMP) and slow inward current have been found (82–84), changes in the levels of cAMP could explain the inhibitory effect of adenosine on slow calcium channels (85–87). This inhibition may contribute, in part, to the

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reduction of calcium fluxes caused by adenosine (88–90). In addition, adenosine may interfere with the fast sodium current (57,85). These effects of adenosine on the slow and fast channels are probably responsible for the shortening of the atrial action potential by adenosine (55,88). In addition, like acetylcholine, adenosine increases K^+ conductance resulting in shortening of atrial action potential hyperpolarization of the membrane of atrial cells (55,86,88).

Mediation of ATP effects. Less is known about the mechanism of action of ATP. Some effects of ATP appear to be the result of its breakdown to adenosine (54,91,92) by ectoenzymes (52). However, there is some evidence (93) that ATP can stimulate P_1 receptors without conversion to adenosine.

The involvement of the vagus in the mechanism of action of ATP was suggested in dogs (5,23,25) and cats (5,6), but not in human beings (19–21), guinea pigs (6) and rabbits (5). A vagal reflex triggered by ATP and not by adenosine could be responsible, at least in part, for the higher potency of ATP found in the heart of certain mammalian species. In addition, the fact that ATP but not adenosine increases the sensitivity of nicotinic cholinergic receptors (94) may also play a part in the different potencies of these two compounds.

In summary, the mechanisms of action of ATP and adenosine are still obscure. Special surface receptors that can be coupled to adenylate-cyclase probably mediate some of the effects of adenosine. The fast breakdown of ATP to adenosine facilitates the action of ATP through adenosine receptors; however, direct stimulation of adenosine receptors by ATP cannot be excluded. Finally, in some species the vagus is involved in the mechanism of action of ATP, which explains the higher potency of ATP than that of adenosine in these species.

Conclusions

Both ATP and adenosine are highly effective in terminating paroxysmal supraventricular tachycardia and have many qualities of the ideal antiarrhythmic drug (95). The very short half-life of these drugs enables repeated administration of increased doses without reaching toxic effects. In addition, ATP and adenosine may be used as a diagnostic tool to differentiate supraventricular tachycardia with intraventricular aberrancy from ventricular tachycardia as well as AV reentrant tachycardia from atrial tachyarrhythmias. Comparative studies of ATP, adenosine and verapamil in human beings are desired to determine the drug of choice for the short-term therapy of paroxysmal supraventricular tachycardia.

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References

1. Drury AN, Szent-Gyorgyi A. The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. J Physiol (Lond) 1929;68:213–37.
2. Drury AN. The physiological activity of nucleic acid and its derivatives. Physiol Rev 1936;16:292–325.
3. Honey RM, Ritchie VT, Thomson WAR. The action of adenosine upon the human heart. Quart J Med 1930;23:485–9.
4. Bielischowsky M, Green HN, Stoner HB. The effects of magnesium and calcium on the physiological properties of certain purine derivatives. J Physiol 1946;104:239–52.
5. Emmelin N, Feldberg W. Systemic effects of adenosine triphosphate. Br J Pharmacol Chemotherap 1948;3:273–84.
6. Wayne EJ, Goodwin JF, Stoner HB. The effect of adenosine triphosphate on the electrocardiogram of man and animals. Br Heart J 1949;11:55–67.
7. Acierno L, Burno F, Burstein F, DiPalma JR. Actions of adenosine triphosphate on the isolated cat atrium and their antagonism by acetylcholine. J Pharmacol Exp Ther 1952;104:264–8.
8. Angelakos ET, Glassman PM. Cardiovascular action of adenosine and other nucleosides. Proc Soc Exp Biol Med 1961;106:762–3.
9. James TN. The chronotropic action of ATP and related compounds studied by direct perfusion of the sinus node. J Pharmacol Exp Ther 1965;149:233–47.
10. Versprille A, Van Duyn CD. The negative chronotropic effect of adenosine derivatives and acetylcholine on the frog and rat hearts. Pflugers Arch 1966;291:288–96.
11. Stafford A. Potentiation of adenosine and the adenine nucleotides by dipyridamole. Br J Pharmacol Chemother 1966;28:218–27.
12. Schondorf H, Rummel W, Pfleger K. Dosis-Wirkungs-Beziehungen Zwischen Koronardurchfluss und Herzfrequenz fur Adenosine. Experientia 1969;25:44–5.
13. Chiba S, Hashimoto K. Difference in chronotropic and dromotropic responses of the SA and AV nodes to adenosine and acetylcholine. Jpn J Pharmacol 1972;22:273–4.
14. Urthaler F, James TN. Effects of adenosine and ATP on AV conduction and on AV junctional rhythm. J Lab Clin Med 1972;79:96–105.
15. Chiba S. Potentiation of the negative chronotropic and inotropic effects of adenosine by dipyridamole. Tohoku J Exp Med 1974;114:45–8.
16. Leclercq JF, Coumel P. Les effets de l'adénosine triphosphate (ATP) sur le noeud sinusal et le noeud auriculo-ventriculaire chez l'homme. Variations selon le lieu d'injection. Coeur Med Interne 1978;17:541–6.
17. Belardinelli L, Belloni FL, Rubio R, Berne RM. Atrioventricular conduction disturbances during hypoxia. Possible role of adenosine in rabbit and guinea pig hearts. Circ Res 1980;47:684–91.
18. Belardinelli L, Mattos EC, Berne RM. Evidence for adenosine mediation of atrioventricular block in the ischemic canine myocardium. J Clin Invest 1981;68:195–205.
19. Favale S, Quagliara D, DiBiase M, Rizzon P. Meccanismo d'azione dell'ATP sub nodo A-V nell'uomo (abstr). In: XLII National Congress. Rome, Italy: Italian Cardiol Society, May 23–26, 1981.
20. Lechat P, Tonet JL, Cohen A, Frank R, Fontaine G, Grosgogeat Y. Mechanism of atrioventricular conduction blockade by adenosine triphosphate (abstr). Circulation 1982;66(suppl II):II–380.
21. Lechat P, Tonet JL, Cohen A, Frank R, Fontaine G, Grosgogeat Y. Mechanism of atrioventricular conduction blockade by adenosine triphosphate. In: Levy S, Gerard R, eds. Recent Advances in Cardiac Arrhythmias. London: John Libbey, 1983:39–40.
22. Belardinelli F, Fenton RA, West A, Linden J, Althaus JS, Berne RM. Extracellular action of adenosine and the antagonism by aminophylline on the atrioventricular conduction of isolated perfused guinea pig and rat hearts. Circ Res 1982;51:569–79.

23. Munoz A, Sassine A, Carabantes G, Lehujeur C, Koliopoulos N, Puech P. Effects of purinergic compounds on AV conduction: experimental studies in anesthetized dogs. In Ref 21:35–8.

24. Favale S, DiBiase M, Rizzo U, Rizzon P. Meccanismo de azione dell'ATP sulla conduzione suprahissiana nell'uomo: ulteriori esperienze (abstr). In: XLIII National Congress. Rome, Italy: Italian Cardiol Society, December 16–19, 1982.

25. Pelleg A, Belhassen B, Terdiman R, Shargorodsky B, Laniado S. Electrophysiological effects of adenosine-triphosphate and adenosine in the canine heart (abstr). Fed Proc 1983;42:731.

26. DiMarco JP, Sellers TD, Berne RM, West A, Belardinelli L. Adenosine: electrophysiologic effects and therapeutic use for terminating paroxysmal supraventricular tachycardia. Circulation 1983;68:1254–63.

27. Somlo E. Adenosine triphosphate in paroxysmal tachycardia (letter). Lancet 1955;268:1125.

28. Komor K, Garas Z. Adenosine triphosphate in paroxysmal tachycardia (letter). Lancet 1955;269:93–4.

29. Latour H, Puech P, Grolleau R, Sat M, Balmes P. L'utilisation de l'adénosine-5'-triphosphate dans le diagnostic et traitement des tachycardies paroxystiques nodales (abstr). Arch Mal Coeur 1968;61:293.

30. Morté G, Waynberger M, Lebars A, Bouvrain Y. L'adénosine triphosphorique dans les tachycardies paroxystiques. Intérêt diagnostique et thérapeutique. Nouv Press Med 1972;1:3057–61.

31. Chimienti M, Salerno JA, Tavazzi L, Ray M. Utilita dell' acido adenosin trifosforico (ATP) nella terapia delle tachicardie reciprocanti (abstr). In: Pozzi, ed. Atti Sixth Congresso ANMCO. Rome, Italy: 1975:331.

32. Greco R, Musto B, Arienzo V, Alborino A, Garofalo S, Marsico F. Treatment of paroxysmal supraventricular tachycardia in infancy with digitalis, adenosine-5'-triphosphate, and verapamil: a comparative study. Circulation 1982;66:504–8.

33. Belhassen B, Pelleg A, Shoshani D, Geva B, Laniado S. Electrophysiologic effects of adenosine-5'-triphosphate on atrioventricular reentrant tachycardia. Circulation 1983;68:827–33.

34. Belardinelli L, West A, Crampton R, Berne RM. Chronotropic and dromotropic effects of adenosine. In: Berne RM, Rall TW, Rubio R, eds. Regulatory Function of Adenosine. Boston: Martinus Nijhoff, 1983:377–96.

35. Szentmiklosi AJ, Nemeth M, Papp JGy, Szegi J. On the possible role of adenosine in the hypoxia-induced alterations of the myocardial electrical and mechanical activity (abstr). In: Sixth Yugoslav Pharmacology Meeting, Ljublijana. 1976:113.

36. Szentmiklosi AJ, Nemeth M, Szegi J, Papp JGy, Szekeres L. On the possible role of adenosine in the hypoxia-induced alterations of the electrical and mechanical activity of the atrial myocardium. Arch Int Pharmacodyn Ther 1979;238:283–95.

37. Belardinelli L, West A, Berne RM. Effects of purines on the A-V node of isolated guinea pig hearts (abstr). Circulation 1982:66(suppl. II):II-380.

38. Kollassa N, Pfleger D, Rummel W. Specificity of adenosine uptake into the heart and inhibition by dipyridamole. Eur J Pharmacol 1970 9:265–8.

39. Degenring FH, Curnish RR, Rubio R, Berne RM. Effect of dipyridamole on myocardial adenosine metabolism and coronary flow in hypoxia and reactive hyperhemia in the isolated perfused guinea pig heart. J Mol Cell Cardiol 1976;8:877–88.

40. Afonso S. Inhibition of coronary vasodilating action of dipyridamole and adenosine by aminophylline in the dog. Circ Res 1970;26:743–54.

41. Giles RW, Wilcken DEL. Reactive hyperaemia in dog heart—interrelations between adenosine, ATP, and aminophylline and effect of indomethacin. Cardiovasc Res 1977;11:113–21.

42. Burnstock G. Purinergic receptors in the heart. Circ Res 1980;46:176–82.

43. Feigl EO. Coronary physiology. Physiol Rev 1983;63:1–205.

44. Lammerant J, Becsei I, Mertens-Strijthagen J, DeSchryver C. Changes in the calculated myocardial oxygen consumption during adenosine infusion versus estimates of developed tension and velocity of contraction. Arch Int Pharmacodyn Ther 1970;186:166–78.

45. Flitney FW, Singh J. Inotropic responses of the frog ventricle to adenosine triphosphate and related changes in endogenous cyclic nucleotides. J Physiol 1980;304:21–42.

46. Szentmiklosi AJ, Takacs I, Szegi J. Studies on the inotropic and chronotropic effects of adenosine. In: Knoll J, Szekeres L, Papp J Gy, eds. Symposium on Pharmacology of the Heart. Budapest: Akademiai Kiado, 1976:81–6.

47. Burnstock G. A basis for distinguishing two types of purinergic receptors. In: Bolis L, Straub RW, eds. Cell Membrane Receptors for Drugs and Hormones: A Multidisciplinary Approach. New York: Raven, 1978:107–18.

48. Perrot B, Faivre G. Action de l'adénosine triphosphorique (ATP) sur les faisceaux accessoires de conduction. Arch Mal Coeur 1982;75:593–604.

49. Perrot B, Faivre G. Effects of adenosine triphosphate on the accessory pathways (abstr). Circulation 1981;64(suppl IV):IV-145.

50. Tajima T, Naito T, Ide M, Dohi Y. Electrophysiological effects of intravenous adenosine triphosphate in patients with paroxysmal supraventricular tachycardia (abstr). In: Proceedings of the VIII Asian Pacific Congress Cardiol, Taipei, Taiwan, November 27–December 2, 1983:222.

51. Davis DF, Gropper AL, Schroeder HA. Circulatory and respiratory effects of adenosine triphosphate in man. Circulation 1951;3:543–50.

52. Williamson JR, Dipietro DL. Evidence for extracellular enzymatic activity of the isolated perfused rate heart. Biochem J 1965;95:226–32.

53. Paddle BM, Burnstock G. Release of ATP from perfused heart during coronary vasodilation. Blood Vessels 1974;11:110–9.

54. Ronca-Testoni S, Borghini F. Degradation of perfused adenine compounds up to uric acid in isolated rat heart. J Mol Cell Cardiol 1982;14:177–80.

55. Hollander PB, Webb JL. Effects of adenine nucleotides on the contractility and membrane potentials of rat atrium. Circ Res 1957;5:349–53.

56. Flitney FW, Singh J. Inotropic responses of the frog ventricle to adenosine triphosphate and related changes in endogenous cyclic nucleotides. J Physiol 1980;304:21–42.

57. Urthaler F, Woods WT, James TN, Walker AA. Effects of adenosine on mechanical performance and electrical activity in the canine heart. J Pharmacol Exp Ther 1981;216:254–60.

58. Needleman P, Minkes MS, Douglas JR. Stimulation of prostaglandin bio-synthesis by adenine nucleotides. Profile of prostaglandin release by perfused organs. Circ Res 1974;34:455–60.

59. Bennet DW, Drury AN. Further observations relating to the physiological activity of adenine compounds. J Physiol 1931;72:288–320.

60. Winbury MN, Papierski DH, Hemmer ML, Hambourger WE. Coronary dilator action of the adenine-ATP series. J Pharmacol Exp Ther 1953;109:255–60.

61. Berne RM. Cardiac nucleotides in hypoxia: possible role in regulation of coronary blood flow. Am J Physiol 1963;204:317–22.

62. Berne RM. Myocardial blood flow: metabolic determinants. In: Zelis R, ed. The Peripheral Circulation. New York: Grune & Stratton, 1975:117–9.

63. Verhaeghe RH, Vanhoutte PM, Shepherd JT. Inhibition of sympathetic neurotransmission in canine blood vessels by adenosine and adenine nucleotides. Circ Res 1977;40:208–15.

64. Shepherd JT, Vanhoutte PM. Local modulation of adrenergic neurotransmission. Circulation 1981;64:655–66.

65. Schrader J, Baumann G, Gerlach E. Adenosine as inhibitor of myocardial effects of catecholamines. Pflugers Arch 1977;372:29–35.

66. Belardinelli L, Vogel S, Linden J, Berne RM. Antiadrenergic action of adenosine on ventricular myocardium in embryonic chick hearts. J Mol Cell Cardiol 1982;14:291–4.

67. Burnstock G. Purinergic receptors. J Theor Biol 1976;62:491–503.

68. Brown C, Burnstock G, Cusack NJ, Meghji P, Moody CJ. Evidence for stereospecificity of the P_1-purinoceptor. Br J Pharmacol 1982;75:101–8.

69. Wolff J, Londos C, Cooper DMF. Adenosine receptors and the regulation of adenylate cyclase. Adv Cyclic Nucleotide Res 1981;14:199–214.

70. Londos C, Cooper DMF, Wolff J. Subclasses of external adenosine receptors. Proc Natl Acad Sci USA 1980;77:2551–4.

71. VanCalker D, Muller M, Hamprecht B. Adenosine regulates via two different types of receptors the accumulation of cyclic AMP in cultured brain cells. J Neurochem 1979;33:999–1005.

72. Schutz W, Tinsl E. Evidence against adenylate cyclase-coupled adenosine receptors in the guinea pig heart. Eur J Pharmacol 1981;76:285–8.

73. Olsson RA, Davis CJ, Khairi EM, Patterson RE. Evidence for an adenosine receptor on the surface of dog coronary myocytes. Cir Res 1976;39:93–8.

74. Schrader J, Nees S, Gerlach E. Evidence for a cell surface adenosine receptor on coronary myocytes and atrial muscle cells. Pflugers Arch 1977;369:251–7.

75. Burnstock G, Meghji P. Distribution of P_1- and P_2-purinoceptors in the guinea pig and frog heart. Br J Pharmacol 1981;73:879–85.

76. Evans DB, Schenden JA, Bristol JA. Adenosine receptors mediating cardiac depression. Life Sci 1982;31:2425–32.

77. Collis MG. Evidence for an A_1 adenosine receptor in the guinea-pig atrium. Br J Pharmacol 1983;78:207–12.

78. Hughes PR, Stone TW. Inhibition of purines of the inotropic action of isoprenaline in rat atria. Br J Pharmacol 1983;80:149–53.

79. Rosen MR, Danilo P Jr, Weiss RM. Actions of adenosine on normal and abnormal impulse initiation in canine ventricle. Am J Physiol 1983;244:H715–21.

80. Szentmiklosi AJ, Nemeth M, Szegi, Papp JGy, Szekeres L. Effect of adenosine on sinoatrial and ventricular automaticity of the guinea pig. Arch Pharmacol 1980;311;147–9.

81. Endoh M, Maruyama M, Taira N. Adenosine-induced changes in rate of beating and cyclic nucleotide levels in rat atria: modification by islet activating protein. In: Daley JW, Kuroda Y, Phillis JW, Shimizer H, Vi M, eds. Physiology and Pharmacology of Adenosine Derivatives. New York: Raven, 1983:127–42.

82. Tsien RW. Adrenaline-like effects of intracellular iontophoresis of cyclic AMP in cardiac Purkinje fibers. Nature 1973;245:120–2.

83. Reuter H. Localization of beta adrenergic receptors and the effects of noradrenaline and cyclic nucleotides on action potentials, ionic currents and tension in mammalian cardiac muscle. J Physiol 1974;242:429–51.

84. Schneider JA, Sperelakis N. Slow Ca^{2+} and Na^+ responses induced by isoproterenol and methylxanthines in isolated perfused guinea pig hearts exposed to elevated K^+. J Mol Cell Cardiol 1975;7:249–73.

85. Schrader J, Rubio R, Berne RM. Inhibitor of slow action potentials of guinea-pig atrial muscle by adenosine: a possible effect of Ca^{2+} influx. J Mol Cell Cardiol 1975;7:427–33.

86. Goto M, Vatani A, Tsuda A. Stabilizing effects of adenosine on the membrane currents and tension components of the bullfrog atrium. Jpn J Physiol 1978;28:611–25.

87. Belardinelli L, Rubio R, Berne RM. Blockade of Ca^{2+} dependent rat atrial slow action potentials by adenosine and lanthanum. Pflugers Arch 1979;380:19–27.

88. DeGubareff T, Sleator W. Effects of caffeine on mammalian atrial muscle and its interactions with adenosine and calcium. J Pharmacol Exp Ther 1965;148:202–14.

89. Guthrie JR, Nayler WG. Interaction between caffeine and adenosine on calcium exchangeability in mammalian atria. Arch Int Pharmacodyn Ther 1967;70:249–55.

90. Grossman A, Fuzchgott RF. The effects of various drugs on calcium exchange in isolated guinea pig left auricle. J Pharmacol Exp Ther 1974;145:162–72.

91. Hopkins SV. The action of ATP in the guinea pig heart. Biochem Pharmacol 1973;22:335–9.

92. Willemot J, Paton DM. Metabolism and presynoptic inhibitory activity of 2′, 3′ and 5′-adenosine nucleotides in rat vas deferens. Arch Pharmacol 1981;317:110–4.

93. Collis M, Pettinger SJ. Can ATP stimulate P_1-receptors in guinea pig atrium without conversion to adenosine. Eur J Pharmacol 1982;81:521–9.

94. Akasu T, Hirai K, Koketsu K. Increase of acetycholine receptor sensitivity by ATP. Br J Pharmacol 1981;74:505–7.

95. Dreifus LS, Ogawa S. Quality of the ideal antiarrhythmic drug. Am J Cardiol 1977;39:466–7.