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 Title : HYPOTENSIVE ACTION OF ADENINE COMPOUNDS
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Introduction. Unlike other peripherally active hypotensive agents, adenosine (Ad) and adenosine triphosphate (ATP) not only cause potent vasodilation but also negative chronotropic and inotropic effects on the heart. The nature of these cardiovascular actions has not been well understood but several mechanisms have been proposed: 1) Neural components¹ a) ATP directly stimulates the medullary vagal center; b) ATP has a veratrum-like effect (Bezold-Jahrisch reflex). 2) Direct action on the heart and vascular smooth muscle. However, most studies relating the cardiac and vascular components have been done in vitro or in isolated organs. Thus, the present study was undertaken in an attempt to better elucidate the primary mechanism of the hypotensive action of Ad and ATP in the anesthetized intact animal.

Methods and Results. Several experimental models in different species such as cat, rabbit and dog were used. They were divided into three groups. The trachea was intubated and ventilation was controlled to keep PaCO₂ 31±4 SE. Arterial blood pressure (BP) was monitored from a femoral artery and heart rate (HR) was sensed either from BP or EKG (lead II). Femoral or ear veins were used for administration of fluids and drugs. Ad or ATP were administered intravenously (IV) as a single bolus or by constant infusion. (Notice that the effects of Ad and ATP have been found to be almost identical).

Group I. The vagal component was tested in 10 cats (pentobarbital 35 mg/kg IV); 12 rabbits (halothane 1%) and 5 dogs (morphine 30 mg IM and chloralose 80 mg/kg IV). Hypotensive effects of ATP were compared before and after administration of atropine (0.03-0.05 mg/kg IV) or bilateral vagotomy. IV injection of ATP (0.1-10 mg/kg) caused a dose-related hypotension with variable changes in HR. Pretreatment with atropine or vagotomy and carotid artery ligation modified the magnitude of ATP induced hypotensive responses to some extent, but it did not completely abolish it in any of the experiments.

Group II. Nerve action potential was measured from the preganglionic cervical sympathetic fibers (CSN) and from the cervical efferent vagal fibers (VE) in 7 cats and in 6 rabbits (pentobarbital 35 mg/kg IV and gallamine 2-5 mg/kg IV). As shown in Fig. 1, immediately after IV bolus injection of ATP, a transient but significant depression of CNS and activation of VE were observed and these changes were followed by profound hypotension and bradycardia thereafter.

Group III. Administration of aminophylline (10 mg/kg IV) during constant infusion of Ad (1 mg/kg/min) in 5 rabbits (halothane 1%) and 4 dogs (halothane 1%) caused immediate and marked antagonistic effects on the HR but had little effect on the blood pressure (Fig. 2).

Conclusion. The results of the present studies indicate that the primary mechanism of Ad or ATP induced hypotension resides mainly in the periphery (vascular and cardiac components) rather than in the neural components since vagotomy and ligation of the carotid artery could not completely abolish the hypotensive response. Moreover, the negative chronotropic action of Ad was effectively antagonized by aminophylline which is known to be an inhibitor of phosphodiesterase; these findings further suggest that the effect of adenine compounds may have a close interaction with the cyclic AMP system.

Reference. Emmelin N, Feldberg W: Systemic effects of adenosine triphosphate. *Br J Pharmacol* 3: 273-284, 1948.

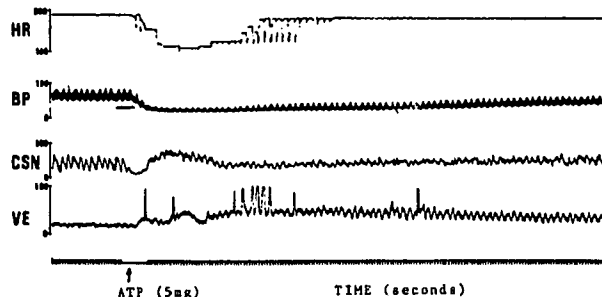


Figure 1. HR: beats/min, BP: torr, CSN: integrated cervical sympathetic nerve discharges, VE: integrated cervical efferent vagal nerve discharges.

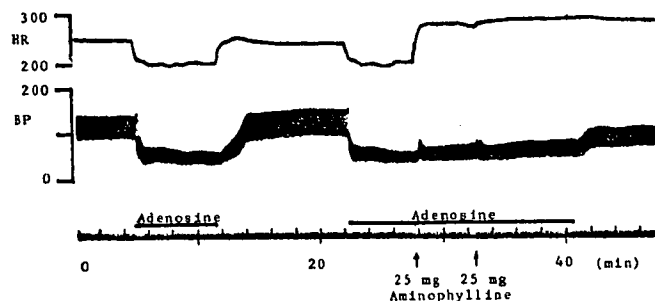


Figure 2. HR: beats/min, BP: torr