Renal Effects of Adenosine
and Their Inhibition by Theophylline in Dogs* **

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Summary. The action of adenosine on renal blood flow and kidney function in dogs was studied with bolus injections and infusion of adenosine into the renal artery. Simultaneous infusions of theophylline, \(1 - 5 \times 10^{-4}\) mol/min into the renal artery which did not affect renal function by itself inhibited the adenosine induced vasoconstriction. From the bolus injection studies a dose response curve (DRC) was constructed. Theophylline shifted the DRC to the right in a parallel manner. \(pA_2 - pA_{10}\) was 0.98 indicating that theophylline inhibition of the adenosine effects may be interpreted as a competitive antagonism. Infusions of adenosine (0.3--1.1 \(\mu\)mol/min) caused a reduction of urine volume, sodium excretion and glomerular filtration rate (GFR). The decrease of GFR after adenosine infusion by 31.4% could be diminished by theophylline. It is suggested that adenosine action is based mainly on a constriction of the vasa afferentia in the outer zone of the cortex.

Key words: Renal Hemodynamics — Adenosine — Theophylline.

The vessels of brain, heart, muscles and intestine dilate markedly after administration of adenosine. Isolated strips of the interlobular artery of the kidney relax after adenosine (Walter and Bassenge, 1968). However, adenosine injected into the renal artery produces a marked decrease of renal blood flow. Thurau (1964) observed in dogs fed with low sodium diet a decrease of RBF after adenosine infusion into the renal artery. Hashimoto (1971) reported an increase of renal vascular resistance after adenosine infusion. Tagawa and Vander (1970) demonstrated a decrease of GFR after infusion of adenosine into the renal artery of dogs. It was of interest to study the effect of theophylline on renal adenosine effects since theophylline is able to inhibit the dilating potency of adenosine in the coronary artery (Afonso, 1970; Schaumann et al., 1970).


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Methods

Experiments were performed in 11 mongrel dogs of either sexes with a body weight of 13—29 kg (mean 22.6 kg). Anesthesia was started with pentobarbital (25—30 mg/kg) and continued as required with 1% chloralose. Respiration was spontaneous. A forelimb vein was cannulated for infusion of saline and creatinine. Blood pressure was recorded from the femoral artery with a Statham pressure transducer P23Db. The left renal artery was exposed retroperitoneally by a flank incision. After careful preparation of the kidney hilus, avoiding damage of the renal nerves, an electromagnetic flow meter (Statham) was placed around the renal artery. Proximal of this flow meter a Y-shaped cannula was inserted with its tip pointing towards the aorta. One inlet of the cannula was connected with a tube, inner diameter 0.5 mm, for single injections of adenosine, the other was connected with a tube for infusion of theophylline by means of an infusion pump (Perfusor, Braun). Injections of lissamine green resulted in a homogeneous coloration of the whole kidney indicating a good mixture of the injected volume with the streaming blood. Urine was collected separately from both ureters. One hour after the end of preparation the experiment was started. Adenosine, 1—160 nmol in 0.20 ml saline was injected within 1 sec. One dose of adenosine was injected 2—3 times with an interval of 3—5 min. There was an excellent reproducibility of the response of RBF to adenosine. The inhibition of the adenosine effects by theophylline was observed during 15—30 min infusion of theophylline. Glomerular filtration rate (GFR) was estimated as creatinine clearance in 6 min collection periods. Creatinine was measured with alkaline picrate reaction (Phillips et al., 1943). Sodium was measured by flame photometry.

The effectiveness of single doses of adenosine to decrease the mean RBF was calculated from the peak to preinjection level as percent decrease of RBF per 100 g kidney weight. The pA2-value (Schild, 1947) was calculated from the logarithm of the dose ratio in presence (B) and absence (A) of the antagonist. The dose ratio was obtained from the half maximal response (Bacq, 1971):  

$$pA_2 = - \log[B] + \log \left( \frac{[A_{50}B]}{[A_{50}]} - 1 \right)$$

$A_{50} =$ is the agonist concentration which produces 50% of the maximal effect in absence of the antagonist;

$A_{50}B =$ is the agonist concentration which produces 50% of the maximal effect in presence of the antagonist;

$B =$ is the antagonist concentration.

When $[A_{50}B] = 2 \cdot [A_{50}]$, then $pA_2 = - \log[B] = - \log K_B$. Under this condition the pA2-value equals the dissociation constant of the antagonist-receptor complex according to Bacq (1971).

Substances. Adenosine was purchased from Boehringer, Mannheim, theophylline from Merck.

Statistics. Experimental data were expressed as their mean ± standard error of the mean. Regression line was calculated by the method of the least squares. Significance was calculated with the Student-test.

Results

Studies on Renal Blood Flow. The original registration curve in Fig.1 shows that injections of 4 or 16 nmol adenosine caused a marked decrease of RBF. The maximal effect is reached within 3.5 sec. This rapid reaction of RBF to adenosine can be seen best when pulsation of RBF are recorded. No initial dilation occurred. For calculating the dose