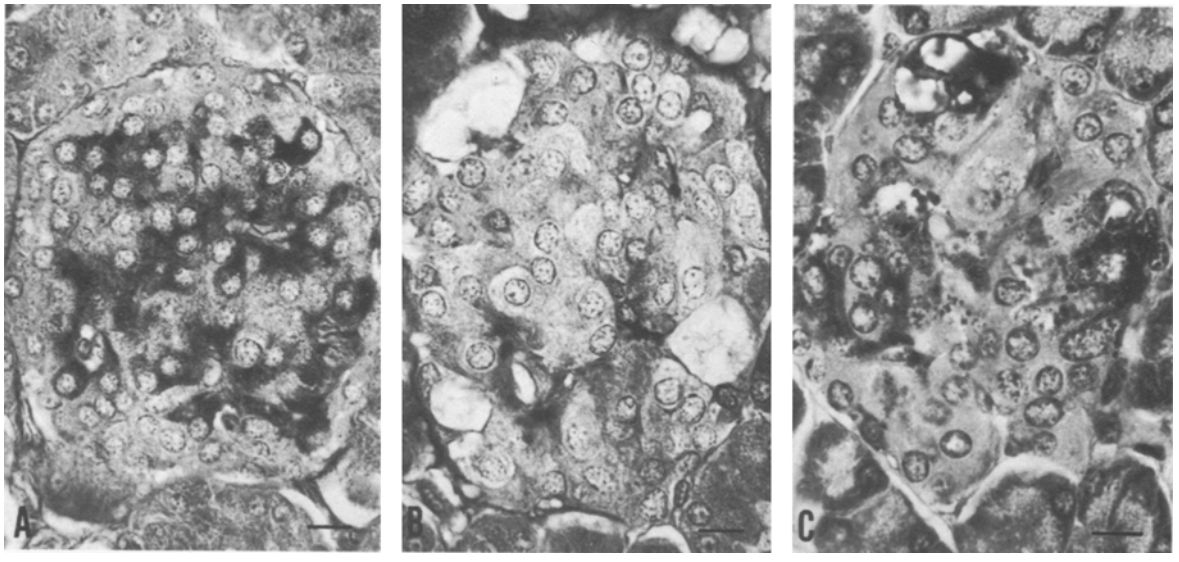

Fig. 3. Pancreatic islets from a normal Chinese hamster (A), and from a MSG-treated hamster (B and C) 30 weeks after the treatment. In the normal pancreatic islet, B cells are well granulated. Islets from the treated hamster show degranulation and vacuolation of B cells, and accumulation of glycogen. Immersion fixation with saturated picric acid containing 2.4% glutaraldehyde and 4% acetic acid. Sections were stained with aldehyde-fuchsin combined with kernechtrot and one-step trichrome (A and B) and the PAS method (C). The horizontal bar represents 10 μm.

The results of the present study show that the VMH lesion is easily induced in new-born Chinese hamsters by the administration of MSG. However, no hypothalamic obesity develops in the VMH-lesioned animals irrespective of their marked increase in food intake. A fact that diabetic syndrome with no obesity is induced with MSG in the Chinese hamster should be emphasized and this new experimental procedure may serve for the study of a possible role of the hypothalamus in the development of diabetes.

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Renal effects of 8-substituted derivatives of adenosine 3′,5′-cyclic monophosphate in dogs[1]

T. Higashio, Y. Abe, M. Miyazaki[2] and K. Yamamoto

Department of Pharmacology, Osaka City University Medical School, Osaka 545 (Japan), 24 April 1979

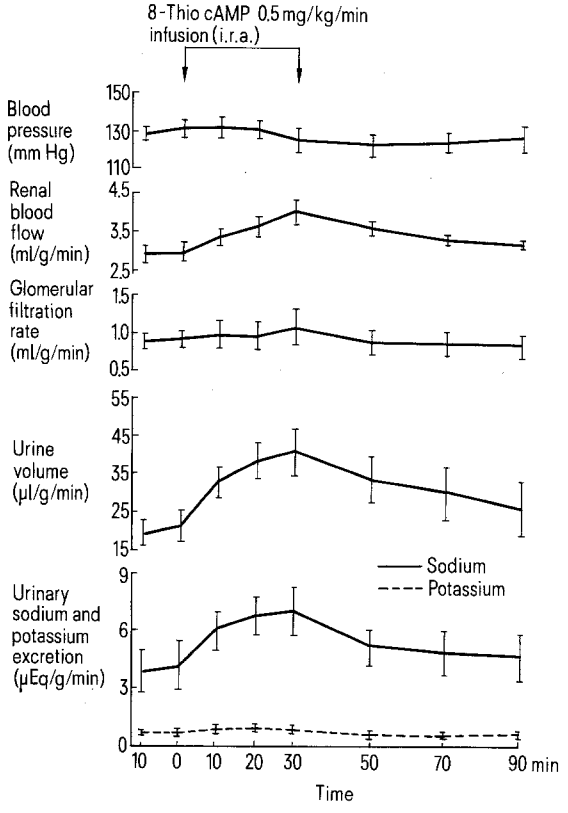
Summary. The renal effects of nine, 8-substituted derivatives of 3′,5′-cyclic monophosphate were studied in anesthetized mongrel dogs. Infusion of the compounds into a renal artery resulted in an increase of renal blood flow without any effect on blood pressure. Diuretic and natriuretic effects are evident with 6 of the 9 derivatives. As these 8-substituted analogues exert renal effects in a manner similar to that seen with the parent nucleotide, cyclic adenosine 3′,5′-monophosphate, they may serve as useful pharmacological agents in vivo.

Using isolated and purified enzyme systems, several 8-substituted derivatives of adenosine 3′,5′-cyclic monophosphate (cAMP) have been shown to possess activating ability for cAMP-dependent protein kinases of bovine brain[3,4] and rat liver[4], and this activating ability is comparable to, or even surpasses, that of the parent nucleotide cAMP. These derivatives also stimulate glycogenolysis in rat liver slices[4], steroidgenesis in adrenal cells and lipolysis in the isolated rat epididymal lipocyte[5]. Matsubara and Imai[6] reported that these 8-substituted compounds produce definite positive inotropic and chronotropic effects in isolated guinea-pig atria. These in vitro studies suggested that the 8-substituted cAMP derivatives may be capable of producing cAMP-like biological effects in vivo. As cAMP has been shown to be involved in water permeability and electrolyte transport in the kidney[7-11], we carried out renal clearance studies in an attempt to screen the renal pharmacological effects of 9 different 8-substituted derivatives of cAMP.

Materials and methods. 27 adult mongrel dogs, weighing 11–14 kg, were anesthetized with pentobarbital (30 mg/kg) given i.v. The left kidney was exposed through a retroperitoneal flank incision and denervated by dissecting all visible nerve fibres and tissue connecting to the renal hilum cephalad to the renal artery. A catheter was introduced into the aorta via a femoral artery for blood pressure (BP) measurements (Nihon-Koden, Type MP-4T). An electromagnetic flow probe was placed on the left renal artery, and the renal blood flow (RBF) was measured using an electromagnetic flowmeter (Nihon-Koden, Type MF-6A). A 23-gauge needle was introduced into the left renal artery proximal to the flow probe for infusion of saline or drug solutions, at a rate of 0.5 ml/min. Clearance experiments were carried out under mild isotonic saline loading as described previously[12]. After 2 consecutive 10-min renal clearance periods, drugs were infused at a rate of 0.5 mg/kg/min for 30 min and urine was collected during the following 3 10-min clearance periods and 3 additional 10-min clearance periods 45, 65 and 85 min after the infusion. Arterial blood samples were obtained at the midpoint of each clearance period, and plasma and urine samples were analyzed for creatinine, sodium and potassium. Sodium and potassium were determined by a flame photometer (Hitachi, Model 205D). Glomerular filtration rate (GFR) was estimated by creatinine clearance.

The drugs used were as follows; 8-hydroxy cAMP, 8-thio cAMP, 8-amino cAMP, 8-bromo cAMP, 8-azido cAMP, 8-methoxy cAMP, 8-methylthio cAMP, 8-dimethylamino cAMP and 8-benzylthio cAMP. These drugs were dissolved immediately before infusion in isotonic saline alkalized with 0.01 N sodium hydroxide solution, and were neutralized to pH 7.4 with 0.01 N hydrochloric acid solution. Only 3 experiments were employed with each derivative as sufficient supplies of the pure compounds had to await synthesis.

Results. The figure depicts the renal effects of 8-thio cAMP as a representive compound of the 9 different, 8-substituted derivatives. The intrarenal infusion of 8-thio cAMP at a rate of 0.5 mg/kg/min resulted in an increase in RBF with no changes in BP and GFR. RBF gradually increased to a maximum after initiation of the infusion then gradually recovered to control levels after completion of the administration. This compound produced a diuresis; urine volume (UV) increased continuously and reached a maximum level 20–30 min after the start of the infusion. There was an increase of about 2-fold, and then a gradual decrease to the control value after cessation of the drug infusion. Urinary sodium excretion ($U_{Na}V$) showed almost the same response pattern as that of UV. $U_{Na}V$ also increased about 2-fold 30 min after the initiation of the infusion. Urinary potas-



Effects of intrarenal arterial infusion of 8-thio cAMP on blood pressure, renal blood flow, glomerular filtration rate, urine volume and urinary sodium and potassium excretion in anesthetized dogs. Values represent the mean ± SE at each clearance period.

Effects of intrarenal arterial infusion of 8-substituted cAMP derivatives (0.5 mg/kg/min) on renal function and urine formation in anesthetized dogs

	BP (mm Hg)	RBF (ml/g · min)	GFR (ml/g · min)	UV (µl/g · min)	$U_{Na}V$ (µEq/g · min)	U_KV (µEq/g · min)
Control	106.0± 3.3	2.60±0.07	0.98±0.22	15.40± 5.23	4.64±1.12	0.52±0.18
8-OH-cAMP	102.0± 4.0	3.18±0.38	0.86±0.18	42.07± 7.50	10.25±1.23	0.82±0.21
Control	132.7± 5.0	2.94±0.24	0.93±0.12	21.60± 5.65	4.21±1.61	0.67±0.18
8-SH-cAMP	125.0± 5.8	3.98±0.32	1.10±0.28	41.09± 6.55	7.17±1.37	0.89±0.06
Control	117.3±12.5	3.61±0.52	0.70±0.18	10.07± 1.18	1.80±0.61	0.38±0.04
8-NH_2-cAMP	116.3±12.7	4.07±0.32	0.67±0.31	12.16± 3.07	1.95±0.49	0.41±0.03
Control	130.7± 9.7	3.02±0.39	0.76±0.24	21.05± 6.40	4.39±0.65	0.49±0.09
8-Br-cAMP	106.3±14.4	4.27±0.53	0.86±0.10	23.76± 2.42	4.60±0.13	0.52±0.12
Control	134.3± 9.4	2.71±0.28	0.71±0.22	9.72± 1.60	2.33±0.66	0.43±0.09
8-N_3-cAMP	116.0± 4.6	4.00±0.22	0.89±0.31	23.74± 4.21	3.88±0.65	0.48±0.06
Control	104.7± 0.9	2.47±0.25	0.86±0.18	11.63± 1.68	3.33±0.33	0.32±0.02
8-OCH_3-cAMP	102.3± 1.8	3.47±0.03	1.02±0.27	21.32± 3.83	5.27±0.65	0.48±0.03
Control	120.7± 6.9	2.46±0.23	0.61±0.10	23.40± 6.92	3.57±2.36	0.73±0.18
8-SCH_3-cAMP	119.0±13.2	3.20±0.08	0.62±0.07	31.68±14.41	6.31±4.15	0.77±0.20
Control	116.0±11.4	2.57±0.48	0.89±0.14	13.23± 2.86	3.51±0.83	0.48±0.18
8-$N(CH_3)_2$-cAMP	109.7±11.2	3.82±0.37	0.91±0.12	56.63± 8.93	9.87±3.72	0.89±0.35
Control	110.7± 8.1	3.12±0.36	0.98±0.14	13.35± 1.30	2.61±0.05	0.42±0.09
8-$SCH_2\varphi$-cAMP	108.3± 6.9	3.67±0.18	0.85±0.10	19.15± 3.01	3.81±0.70	0.49±0.08

All values are mean ± SE (n = 3). BP, blood pressure; RBF, renal blood flow; GFR, glomerular filtration rate; UV, urine volume; $U_{Na}V$, urinary sodium excretion; U_KV, urinary potassium excretion.

sium excretion (U_KV) showed an increase of about 30% of the control value during the 8-thio cAMP administration.
The table summarizes the results obtained with nine 8-substituted derivatives of cAMP. Paired values represent data obtained before and 20–30 min after the initiation of the infusion of each compound. As was the case with 8-thio cAMP, the other derivatives also increased RBF with only a slight effect on BP and GFR. Apparent diuretic, natriuretic and kaliuretic effects were observed with 6 of the 9 derivatives: 8-hydroxy cAMP, 8-thio cAMP, 8-azido cAMP, 8-methoxy cAMP, 8-methylthio cAMP and 8-dimethylamino cAMP.

Discussion. The nine different 8-substituted derivatives of cAMP we examined here were found to increase RBF with essentially no effect on BP, in agreement with the findings using cAMP[13,14]. In general, an increase in intracellular cAMP in smooth muscle cells is associated with a relaxation of the muscle[15]. Muneyama et al.[3] who studied the relative stability of some 8-substituted cAMP derivatives to enzymatic hydrolysis found that these derivatives are fairly resistant to degradation by rabbit kidney phosphodiesterase. In addition, it was apparent that some were inhibitors of cAMP phosphodiesterase. The above findings suggest that the vasodilative effects of the 8-substituted derivatives may be related to an intracellular substitution for cAMP or an increase in cAMP by inhibition of cAMP phosphodiesterase. However, the present study does not rule out the possibility that metabolites of the 8-analogues may mediate the renal vasodilating effects of these compounds, as adenosine is reported to produce renal vasodilation in a manner similar to that seen with cAMP[13].
Though all the 8-substituted derivatives increased RBF, only some produced moderate diuretic and natriuretic effects. A similar discrepancy was also reported between the effects of cAMP and dibutyryl cAMP (DBcAMP) on urine formation[14,16]. We have no explanation for these discrepancies; however, it is noteworthy that DBcAMP, as well as some of the 8-substituted derivatives, is more resistant than cAMP to hydrolysis to 5′-adenosine monophosphate by cyclic nucleotide phosphodiesterase[17], and that an inhibition of phosphodiesterase has been suggested[18].
The 8-analogues induced diuretic and natriuretic effects with little effect on GFR, thus suggesting the renal tubular effects of these derivatives. In fact, the parent nucleotide cAMP may inhibit electrolyte transport in the proximal tubule[7,8,10,11]. Differences in diuretic potency among these derivatives probably reflect the intracellular concentrations of these compounds in the tubules.

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2 Present address: Department of Pharmacology, Shiga University of Medical Science, Ohtsu, Shiga 520-21, Japan.
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Antipyrine metabolism in cancer patients

T. Higuchi[1], T. Nakamura and H. Uchino

Department of Internal Medicine, Shiga Center for Adult Diseases, 328 Moriyama, Moriyma, Shiga 524 (Japan), and The First Division, Department of Internal Medicine, Faculty Of Medicine, Kyoto University, Kyoto 606 (Japan), 27 March 1979

Summary. The metabolism of antipyrine was studied in cancer patients. Antipyrine elimination might be decreased in cancer patients. Increase in antipyrine half-life is not primarily due to the presence of a tumor but rather to the nutritional status and liver function of an individual.

The effects of the presence of some tumors on the hepatic microsomal enzymes that metabolize drugs have been studied extensively in animals[2,3]. These studies show that inhibition of hepatic drug metabolism is observed in tumor-bearing animals[2,3]. In contrast with animal studies, little is known about drug metabolism in humans with cancer. Ambre et al.[4] reported a shortened plasma elimination half-life of antipyrine in patients with lung cancer compared to normal volunteers. In contrast with the findings of Ambre et al.[4], Tschanz et al.[5] recently demonstrated a decreased rate of drug clearance in lung cancer patients. Clinicians treating patients with cancer must realize that neoplasia may influence drug disposition and metabolism markedly since patients usually receive a number of anticancer agents that are metabolized by hepatic microsomal enzymes. Our study was conducted in a series of patients with gastric carcinoma and carcinoma of the pancreas to compare systematically the activities of hepatic microsomal enzyme system in patients with localized carcinoma and in patients with disseminated carcinoma and in control subjects, using antipyrine half-life ($t_{1/2}$) as an index of drug metabolism, and to evaluate the microsomal enzyme system in humans with cancer.
Materials and methods. 4 groups of subjects were chosen for