

Antagonism to the Diuretic Action of SR 720-22 (33869)

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(Introduced by Z. Hadidian)

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Ross and Cafruny (1) showed that the compound Ex 4877 (Fig. 1) was a competitive blocker of the diuretic effects of hydrochlorothiazide. Ex 4877 also blocked the diuretic effect of chlorothiazide provided maximal carbonic anhydrase inhibition was first produced by pretreating a dog with acetazolamide. The diuretic activity of acetazolamide was not antagonized by Ex 4877. In a subsequent study by Small and Cafruny (2), Ex 4877 did not block the diuretic activity of furosemide. It seemed that Ex 4877 was a specific blocker of benzothiadiazines. Since SR 720-22, a diuretic recently described by Belair (3), is not a benzothiadiazine (Fig. 1), the effect of Ex 4877 on SR 720-22 was determined to aid in establishing (i) the specificity of blockade of Ex 4877, and (ii) the mode and site of action of SR 720-22.

Methods. Dogs anesthetized with sodium pentobarbital (30 mg/kg, iv) were used in these experiments. The trachea was intubated. A carotid artery was cannulated, the cannula was connected to a Sanborn pressure transducer and a continuous recording of the blood pressure was made on a Sanborn recorder. The external jugular vein was cannulated for a constant infusion of isotonic saline at the rate of 0.33 ml/kg/min; the infusion was preceded by the intravenous injection of 25 ml/kg of isotonic saline (1).

The Ex 4877 was prepared as a suspension in distilled water. SR 720-22 and furosemide were dissolved in 0.2 N NaOH. The compounds were given intravenously.

Urine was collected at 20-min intervals from an indwelling catheter in the bladder or from silicone rubber tubes placed in the ureters. The urinary concentrations of sodium and potassium were determined with a Perkin-Elmer model 303 atomic absorption spectrophotometer. Chloride concentrations were measured with a Buchler-Cotlove chloridometer.

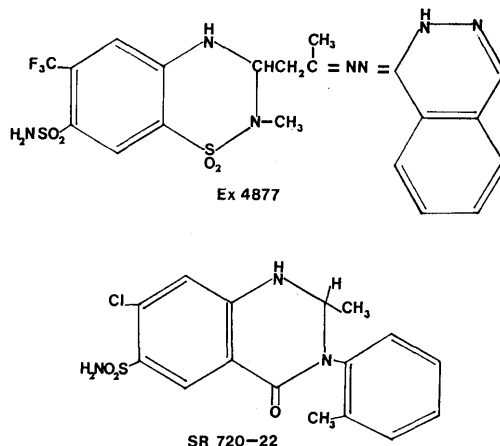


FIG. 1. Structural formulas of Ex 4877 and SR 720-22.

Each experiment was carried out in essentially the same manner. After three 20-min control periods, saline or Ex 4877 was given. Three periods later SR 720-22 was injected. Urine was collected for three additional periods after which furosemide was injected as a positive control.

Because of the small amount of Ex 4877 available, we were not able to carry out as extensive a study as would have been desirable for defining the effects of Ex 4877 on the diuretic actions of SR 720-22. To minimize the problem we applied the findings reported by Ross and Cafruny with respect to the dose, route of administration, and time course of blocking action of Ex 4877 (1).

Results. A well defined diuretic effect occurred in dogs after the intravenous injection of SR 720-22 (0.1–0.5 mg/kg). The effects were maximal during the first 20-min period following the injection of the diuretic and were sustained throughout the second period. By the end of the third period the diuretic effects were decreasing. Furosemide, 1 mg/kg, produced its maximal diuretic effects during the first period. Tables I and II therefore show the results of these tests in

TABLE I. Blockade of the Diuretic Response to SR 720-22.

Dog no.	Dose of SR 720-22 (mg/kg, iv)	Dose of Ex 4877 (mg/kg, iv)	Increase in urinary excretion ^a			
			Volume (ml/20 min)	(meq/20 min)		
				Na	K	Cl
1	0.1	—	23	5.3	0.3	5.7
2	0.1	—	17	3.5	0.1	6.0
3	0.1	—	26	5.7	0.4	5.6
4	0.1	—	19	3.8	0.2	3.7
5	0.5	—	23	5.4	0.1	6.4
6 ^b	0.1	5	26	1.4 ^c	0.10	1.6 ^c
7 ^b	0.1	5	0	0.3 ^c	0.09	0.4 ^c
8 ^b	0.1	5	0	2.5	0.20	3.4
9 ^b	0.5	5	4	0.8 ^c	0.08	0.8 ^c

^a Difference between the last 20-min period before and the first 20-min period after SR 720-22.

^b Ex 4877, 5 mg/kg, was given intravenously 1 hr before SR 720-22.

^c Significant decrease in Na and Cl excretion, $p < 0.05$.

terms of the changes in urinary volume and electrolytes between the first period before and the first period after the injection of SR 720-22 or furosemide.

Ross and Cafruny (1) reported that dogs given 5 mg/kg of Ex 4877 1 or 2 hr before the administration of hydrochlorothiazide did not respond to the diuretic. Accordingly, in our second series of experiments, SR 720-22 was given 1 hr and furosemide 2 hr after 5 mg/kg of Ex 4877. Table I shows that the diuretic effects of SR 720-22 were essentially completely blocked in two dogs and partially blocked in another. There was a questionable effect in a fourth dog. The nature of the block was not determined because of a lack of Ex 4877. There was no significant difference between the diuretic response to furose-

midate in control dogs and in dogs pretreated with Ex 4877 (Table II).

Discussion. It was demonstrated that Ex 4877 blocked the diuretic response to SR 720-22 in dogs. The spectrum of blocking action of Ex 4877 therefore can be considered to include not only benzothiadiazines, but also at least one quinazolinone. Blockade by Ex 4877 of the diuretic effect of SR 720-22 lends support to a tentative conclusion that SR 720-22 exerts its diuretic effect by an action similar to hydrochlorothiazide, made on the basis of: parallel dose-response curves, similar patterns of electrolyte excretion, decreased free water clearance, little or no carbonic anhydrase inhibitory action, a non-specific anti-aldosterone effect, and a diuretic action not blocked by BAL (3).

TABLE II. Effects of Ex 4877 on the Diuretic Response to Furosemide in Dogs.

No. of dogs	Dose of Furosemide (mg/kg, iv)	Dose of Ex 4877 (mg/kg, iv)	Increase in urinary excretion ^a (mean \pm SE)		
			Volume	(meq/20 min)	
				Na	Cl
5 ^b	1	—	105.0 \pm 11.6	12.7 \pm 2.5	13.6 \pm 2.0
4 ^b	1	5 ^c	111.4 \pm 10.2	16.6 \pm 1.7	18.0 \pm 1.5

^a Difference between the last 20-min period before and the first 20-min period after furosemide.

^b These dogs were given SR 720-22 (0.1–0.5 mg/kg, iv) 1 hr before furosemide.

^c Ex 4877 was given 2 hr before furosemide.

Our results agreed with the findings of Small and Cafruny (2) that Ex 4877 does not block the diuretic response to furosemide.

Summary. Ex 4877 blocked the diuretic effects of SR 720-22, a quinazolinone, indicating a broader spectrum of blocking action for Ex 4877 and a similarity in the mode of action between hydrochlorothiazide and SR 720-22. The results support the findings by Small and Cafruny (2) that Ex 4877 does not block the diuretic effects of furosemide.

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The Effect of Glucola, Diet Cola and Water Ingestion on Blood Glucose and Plasma Insulin (33870)

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Kun and Horvath (1) investigated the effect of oral saccharin on carbohydrate metabolism and found that the ingestion of this substance caused a significant fall in blood glucose levels. They suggested that the sweet taste of saccharin stimulated the secretion of insulin via a reflex mechanism involving the sensory fibers from the taste end-plates and the vagus nerve. Emotional and neurogenic influences on blood sugar have been the subjects of repeated investigations (2, 3). Recent experiments indicate that electrical vagal stimulation provokes insulin secretion from the pancreas of anesthetized dogs (4, 5). These findings led us to investigate the effect of a noncaloric, sweet tasting substance on blood glucose and plasma insulin levels.

Methods. Four young healthy male adults who were neither diabetics nor first degree relatives of diabetics were studied. They were told before the experiment that at three sessions they would be given a nutritive liquid to drink and that blood samples would be drawn. After an overnight fast two blood

samples were taken. Each subject was then given, in separate studies, 10 oz of Glucola¹ (equivalent to 107 g of glucose), diet cola (a calorie-free similarly tasting cola drink containing 30 mg of saccharin), or water. They believed both cola drinks to be nutritive. Blood samples were drawn at: 5, 15, 30, 60, 90, and 120 min. Plasma immunoreactive insulin (IRI) was measured by a double antibody method (6) and blood glucose was measured on a Technicon Auto-Analyzer by the method of Hoffman (7).

Results. As shown in Fig. 1, when Glucola was given, plasma insulin levels rose to over 300% of fasting at 5 min and were greater than 500% at 30 min. With both the diet cola and water no significant rise in insulin levels was detected. Blood glucose levels rose to 163% of fasting at 30 min following Glucola, but remained essentially unchanged in the other studies.

Discussion and Conclusions. These results demonstrate that neither the sight nor the taste of a sweet diet cola preparation pro-

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