

Pharmacology of Nicotine: Antipyretic, Renal and Adrenocorticotrophic Effects. (18834)

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Nicotine has antidiuretic activity in the rat (1,2) and in man(1,3). Derivatives of 3-hydroxycinchoninic acid have been shown to be antidiuretic in the dog(4) and rat(2). In the rat, hypophysectomy abolished this effect of nicotine(1), and it has since been found that partial neurohypophysectomy is sufficient to abolish the antidiuretic effect both of nicotine and 3-hydroxycinchoninic acid derivatives in the rat(2).

Because of this similarity and the concurrent work in this laboratory on various effects of the substituted cinchoninic acids, it became of interest to investigate nicotine with regard to some of these other properties. When the cinchoninic derivatives were assayed for antipyretic activity(5), nicotine was included and found highly active. The temperature studies were therefore extended, and renal and adrenocorticotrophic effects of nicotine were also investigated. These comprise the present report.

In all experiments, solutions of nicotine bitartrate in 0.9% saline were used. Figures given refer to the salt.

Antipyretic. Methods were identical with those previously described(5). The data of Table I permit a quantitative estimation of the antipyretic activity of nicotine in the rat. Based on the earlier study(5), nicotine is 60 times as active as salicylic acid and 10 times as active as the most potent of the cinchoninic acid derivatives. Fig. 1 shows that the anti-

TABLE I. Effect of Nicotine on Temperature of the Rat.

Dose, mg/kg	No. rats	Change in temp. (°F) 1 hr after drug
Yeast fever		
5	4	—3.1
2	4	—2.1
.8	8	—1
.3	4	— .2
Saline	9	0
Unfevered		
5	6	—1.9
2	3	— .1
.8	3	+ .2
Saline	5	+ .2

Drug was given subcutaneously in approximately 1 ml of solution.

pyretic effect may also be obtained in the rabbit and dog. The effect on the unfevered rat (Table I) is similar to that of acetanilide (6) and 3-hydroxy-2-phenylcinchoninic acid (5); lowering of temperature is observed at a dose 4-6 times greater than that needed for antipyresis. A survey of the literature does not reveal any occasion when nicotine has been given to a fevered animal and the temperature recorded. On the normal animal there are scanty and inconclusive early reports on doses ranging from homeopathic to lethal, where both rises and falls in temperature had been noted. Some of these data were reviewed by Lestschinskaja(7). She found that the rabbit and the guinea pig usually responded to subcutaneous injection of 1 mg/kg with a fall in temperature.

Renal. The antidiuretic effect of nicotine has not previously been reported in the dog, nor has there been any study of creatinine clearance following nicotine. In 5 dogs, the minimum dose for sharp antidiuresis was 0.05-0.20 mg/kg. In these experiments the ani-

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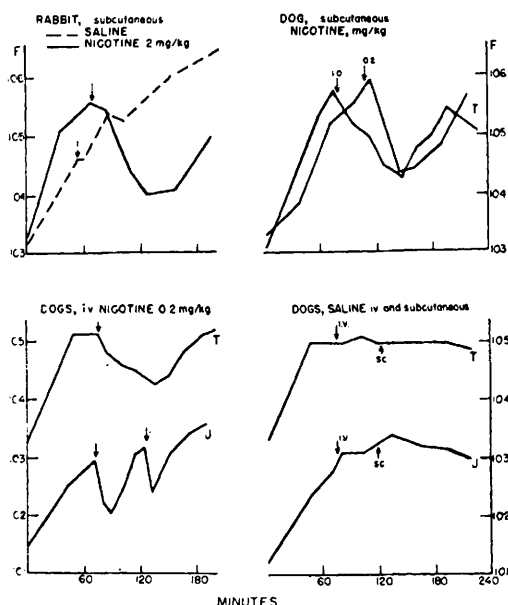


FIG. 1. Effect of nicotine on the febrile rabbit and dog. Fever induced by intravenous Pyromen at 0 time. Arrow at drug or saline. Dogs are identified by letter.

corresponds to a vascular effect in this period. Following this, however, and at the lowest points of urine flow, creatinine clearance is essentially normal. Similar results were obtained with 3 other dogs. Creatinine was determined by the Jaffe reaction(8). Nicotine antidiuresis therefore appears to be largely independent of creatinine clearance, which is probably a measure of glomerular filtration in the dog. Like 3-hydroxy-2-phenylcinchoninic acid(4), nicotine appears to increase the tubular reabsorption of water in the dog. In connection with previous studies from this laboratory(9), it was of interest to find whether nicotine affected the renal excretion of phenol red. After the intravenous injection of 6 mg of phenol red and 0.2 mg/kg of nicotine, the amount of dye excreted in 1 and 2 hours was measured. Figures in parenthesis are for phenol red without nicotine. At these times respectively Dog J excreted a total of 2.7 (2.9) and 3.4 (3.8) mg; Dog T a total of 3.6 (3.7) and 4.1 (4.2) mg. Unlike the

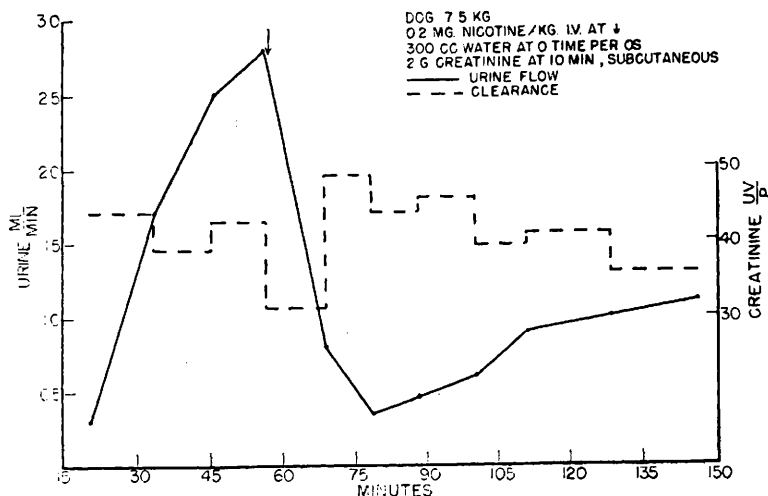


FIG. 2. Effect of nicotine on water diuresis and creatinine clearance in the dog.

imals were fasted for 16-18 hours, 40 ml water per kilogram was given at zero time, and nicotine injected intravenously (approximately 2 ml in 40 seconds) during diuresis. Fig. 2 is a typical curve. This experiment includes creatinine clearance, performed in the usual manner. It may be noted that immediately after nicotine injection there is a transient fall in clearance, which probably

cinchoninic acid derivatives(9), therefore, nicotine does not appear to inhibit the renal excretion of phenol red.

8. War Department Technical Manual (TM 8-227): Methods for Laboratory Technicians, 1947, p196.

9. Dearborn, E. H., *Bull. Johns Hopkins Hosp.*, 1950, v54, 346.

TABLE II. Effect of Nicotine on Adrenal Ascorbic Acid in the Rat.

Normal			Hypophysectomized		
mg ascorbic acid/100 g adrenal $\pm$ S. E. of mean					
No. rats			No. rats		
Saline	13	403 $\pm$ 17	Saline	8	329 $\pm$ 14
Nicotine	6	335 $\pm$ 11	Nicotine	6	353 $\pm$ 13
2 mg/kg			4 mg/kg		
			ACTH	4	199 $\pm$ 11
			10 mg/kg		

All drugs given subcutaneously 2 hr before removal of adrenals.

Adrenocorticotrophic. Using the same techniques and criteria as previously described(10), the effect of low doses of nicotine on adrenal ascorbic acid in normal and hypophysectomized male Sprague-Dawley rats was studied. Table II gives the results. In the intact animal the difference between nicotine and saline is significant ($P < .01$); since hypophysectomy abolishes this effect it appears that nicotine like cinchoninic acid derivatives and a number of other drugs(10), stimulates the adrenal by a pathway which includes the adeno-hypophysis. In the operated animals, inspection at autopsy with a low power lens revealed total absence of the anterior lobe and a variable amount of neural stalk and lobe.

Discussion. Brief mention may be made of the relation that the above doses bear to the lethal or to those that give prominent side effects. At the range used in the rat there were occasional bouts of irregular breathing 15-30 minutes after injection. No other abnormalities were noted. At 15 mg/kg subcutaneously, tachypnea was observed; at 30-100 mg/kg there were brief convulsions and partial collapse, with recovery. In the dog the order of dose used above (0.1 mg/kg) caused panting and some salivation for about 30-60 seconds after intravenous injection. No signs were seen after subcutaneous injection.

Four mg/kg intravenously caused convulsion and collapse, with recovery. The intravenous L.D.₅₀ in the dog is reported as 5 mg/kg, presumably as free base(11). In the rabbit slight increase in respiratory rate was noted at 1 mg/kg intravenously, but not subcutaneously. The intravenous L.D.₅₀ in the rabbit is 6.2 mg/kg, presumably as free base(12). In these species therefore the doses used are about 1/25-1/50 of the convulsive or lethal.

It therefore appears that in relatively low doses nicotine shares the antipyretic, anti-diuretic, and adrenocorticotrophic effects previously reported for 3-hydroxycinchoninic acid and its derivatives.

Summary. 1. Nicotine lowers the temperature of the fevered rat, rabbit and dog. 2. In addition to the previously described anti-diuretic effect of nicotine in rat and man, the present experiments indicate high activity in the dog, and independence of this effect from changes in glomerular filtration rate. Nicotine did not lower the renal excretion of phenol red in the dog. 3. Nicotine lowers the concentration of ascorbic acid in the rat adrenal. This effect is completely abolished by total adeno-hypophysectomy.

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