CHANGES PRODUCED BY ANALGESICS IN THE SENSITIVITY OF THE KIDNEYS TO ANTIDIURETIC HORMONE

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The effect of intravenous injection of pituitrin P (0.1 ml/kg) on the kidneys was studied in dogs receiving analgesics (acetylsalicylic acid 100 mg/kg; sodium salicylate 200 mg/kg; phenacetin 80 mg/kg) for 6 months. Under the influence of these analgesics the response of the kidneys to injection of pituitrin was altered. The inhibition of diuresis was less marked and excretion of osmotically free water was greater in the experimental dogs than in the controls. These changes indicate a decrease in the sensitivity of the tubular epithelium to the antidiuretic hormone under the influence of the analgesics.

KEY WORDS: antidiuretic hormone; salicylates; kidneys.

In 1953 Spuhler and Zollinger [12] described lesions of the kidneys caused by the prolonged administration of analgesics containing phenacetin. Cases of phenacetin nephropathy also were observed by other workers under clinical and experimental conditions [5]. One manifestation of these disturbances is a change in the concentrating power of the kidneys [7]. Renal disturbances have been associated in recent years with the taking of salicylates also [8].

The effect of phenacetin and salicylates on the sensitivity of the kidneys to antidiuretic hormone (ADH), a substance of great importance in the mechanisms of concentration and dilution of the urine, was investigated.

EXPERIMENTAL METHOD

Experiments were carried out on 60 adult mongrel male dogs divided into four groups. The animals of group 1 received phenacetin (80 mg/kg) by mouth daily for 6 months, group 2 received 100 mg/kg acetylsalicylic acid daily, and group 3 received sodium salicylate (200 mg/kg daily). The dogs of group 4 acted as the control. The minute diuresis, glomerular inulin filtration, and clearance of osmotically free water were investigated [1]. Inulin in the plasma and urine was determined by the resorcin method [6] and the osmolarity of the plasma and urine by a cryoscopic method [2]. All indices were recorded before and 10-20 min after intravenous injection of pituitrin P (0.1 ml/kg).

EXPERIMENTAL RESULTS AND DISCUSSION

The results are given in Table 1.

Injection of pituitrin P into dogs taking salicylates or phenacetin gave a less marked antidiuretic effect than in the control animals. The reduction of diuresis in the experimental animals was only a little over 20% of the initial level, compared with over 40% in the control. This difference was not due to a disturbance of the filtration power of the kidneys, for the inulin clearance was virtually identical in the control and experimental animals. Consequently, the smaller decrease in diuresis following injection of pituitrin P into dogs taking salicylates or phenacetin depended on corresponding changes in the reabsorption of water in the tubular portion of the nephron. Clear differences were in fact found between the tubular re-

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TABLE 1. Effect of Pituitrin P on Diuresis (V), Glomerular Filtration (C_{in}), Tubular Reabsorption of Water (R_{H_2O}), Osmolarity of the Urine (U_{osm}), Osmotic Clearance (C_{osm}), and Clearance of Osmotically Free Water (C_{H_2O}) in Dogs (M ± m)

Experimental conditions	Time of admin. of pituitrin P relative to salicylates and phenacetin	Index					
		V (ml/min)	C_{in} (ml/min)	R_{H_2O} in %	U_{osm} (mosm/kg)	C_{osm} (ml/min)	C_{H_2O} (ml/min)
Control	before administ.	11,7±0,4	83,8±1,4	86,2±3,0	68,9±2,7	2,6±0,2	9,1±0,2
	after administ.	6,3±0,3	80,5±1,9	92,2±0,7	204±12	4,2±0,2	2,1±0,3
Acetylsalicylic acid	before administ.	12,8±0,5	70,6±3,3	83,8±2,5	70,6±4,9	3,1±0,2	9,7±0,7
	after administ.	9,3±0,3*	79,4±2,6	88,4±1,9*	144±5*	4,3±0,6	5,0±0,4*
Sodium salicylate	before administ.	12,3±0,2	81,9±2,0	85,0±2,7	82,6±2,7	3,0±0,1	9,3±0,4
	after administr.	9,5±0,4*	80,1±2,8	88,0±0,6*	155±8*	5,3±0,3	4,2±0,3*
Phenacetin	before administr.	12,5±0,5	82,0±3,5	84,9±3,1	76±3,6	2,9±0,3	9,6±0,5
	after administr.	9,6±0,4*	80,8±4,0	88,1±1,0*	149±7*	4,7±0,4	4,9±0,3*

*Index differs significantly from corresponding control index ($P < 0.05$).

absorption of water in the control and experimental dogs. In addition, injection of pituitrin P into dogs taking salicylates or phenacetin was followed by a smaller decrease in the clearance of osmotically free water.

ADH is known to be the chief regulator of the tubular reabsorption of water and the clearance of osmotically free water. Since the experimental conditions required the administration of strictly equal doses of pituitrin it can be concluded that the differences observed were due to changes in the sensitivity of the kidneys to ADH.

One of the primary reactions in the formation of the hormone–tubular cell complex is interaction between SS-groups of ADH and SH-groups of the receptor, with subsequent stimulation of various intracellular systems [3, 9]. Some phenacetin metabolites react easily with substrates containing SH-groups [4]. The possibility thus cannot be ruled out that during prolonged administration of phenacetin, a substance excreted mainly by the kidneys, the chemical receptor of the tubular cells with which ADH reacts may change.

Excretion of water free from osmotic substances is largely determined by the state of the system on active sodium transport in the epithelium of the renal tubules. This system is highly sensitive to ATP deficiency [3]. Experiments have shown that salicylates uncouple oxidative phosphorylation [4, 13] and inhibit glycolysis [11]. This fact may be connected somehow with the development of a reactivity of the kidneys to ADH and the disturbance of the excretion of osmotically free water under the influence of salicylates. Although the permeability of the distal tubules, a change in which could also bring about changes in the excretion of osmotically free water, was not investigated in the present experiments, the possibility of such an effect of phenacetin was not confirmed by experiments on the code urinary bladder [10]. As regards salicylates this question still remains open.

The results thus point to changes in the sensitivity of the kidneys to pituitrin in dogs taking salicylates or phenacetin for a long time. No significant difference was found between the action of salicylates and phenacetin, although the essential biochemical mechanism of the development of areactivity of the renal tubules to ADH may differ for each of these preparations.

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