Inhibition of Leukocytic Pyrogen-Induced Fever by Intracerebroventricular Administration of Salicylate and Acetaminophen in the Cat[1] (36467)

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Intravenous injection of sodium salicylate has been shown to inhibit the pyrogenic action of leukocytic pyrogen (LP) given iv in the rabbit (1, 2), cat (3), and human (4). A similar antipyretic effect has also been demonstrated with acetaminophen in the cat (3). Cooper *et al.* (1) were unable to reduce the pyrogenicity of LP injected into the lateral cerebral ventricle of the rabbit with iv administration of salicylate and suggested that salicylate might exert its antipyretic effect by impairing access of LP to appropriate sites in the central nervous system. However, evidence for a more direct antipyretic action within the central nervous system has since been provided by reports of antipyresis following injection of sodium salicylate into the cerebrospinal fluid and preoptic or midbrain regions in the rabbit (2, 5). In the studies reported below, the effects of lateral ventricular administration of sodium salicylate and acetaminophen on fever induced by iv injection of LP were determined in the cat. The results indicate that both agents exert an antipyretic effect centrally in this species.

Methods. Cats weighing between 2.4 and 5.9 kg were used. Procedures for care and feeding of these animals, for recording body temperature chronically from the retroperitoneal space, for making iv or lateral cerebral ventricular injections, for collection of LP from acute peritoneal exudate cells, for sterilization of glassware, and for otherwise avoiding contamination have been described previously (3, 6). Ambient temperature was maintained at 24 ± 1°. Antipyretics or control saline injections were given intraventricularly at 9:30 AM in a volume of 0.10 ml. All studies utilized a crossover design in which these intraventricular injections were made in randomly determined order. LP was injected iv at 10:00 AM and was flushed in with 1.0 ml of saline solution. A number of different batches of LP were used, but for any given pair of tests the cat received the same amount of the same batch. Results were analyzed by the Wilcoxon matched-pairs signed-ranks test (7). In experiments on possible hypothermic effects of the antipyretics, identical procedures were followed except that no LP was given at 10:00 AM. The average of temperature readings at 9:00, 9:15, and 9:30 AM was used as the base line from which changes were measured. Individual responses were plotted on graph paper with time (1 in. = 1 hr) on the abscissa and temperature change (1 in. = 1°) on the ordinate. The area, in square inches, between the appropriate segment of the curve and the base line was determined to give a thermal response index (TRI). One unit of TRI is equivalent to a 1° change lasting for 1 hr. TRI's were determined for both the 2- and 3-hr periods beginning at 10:00 AM.

Results. Intraventricular injection of sodium salicylate in doses from 0.25 to 1.00 mg produced significant reductions in TRI's and peak responses to LP (Table IA) without causing significant hypothermic effects over the same time periods in animals which had not received LP (Table IIA). Figure 1 shows mean responses to LP after saline or selected doses of the antipyretics. Only 0.50 and 1.00 mg doses of acetaminophen produced statis-

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TABLE I. Effect of Antipyretics Injected into the Lateral Cerebral Ventricle on Fever Induced by Leukocytic Pyrogen Administered iv.

Antipyretic	Dose[a] (mg)	2-hr TRI ($\Delta° \times$ hr)[b]	p[c]	3-hr TRI ($\Delta° \times$ hr)	p	Peak (°)	p
A. Sodium salicylate	0.00	1.29 (0.59–2.20)	$<.01$	1.40 (0.42–2.39)	$\leq.01$	1.1 (0.7–1.8)	$<.01$
	1.00	0.59 (—0.11–1.24)		0.64 (—0.44–1.54)		0.7 (0.1–1.2)	
	0.00	0.94 (0.27–1.63)	$\leq.01$	1.03 (—0.09–1.96)	$\leq.05$	0.9 (0.6–1.4)	$<.05$
	0.50	0.51 (0.13–1.12)		0.39 (—0.45–1.37)		0.6 (0.3–1.1)	
	0.00	1.44 (0.78–1.85)	$<.01$	1.51 (0.99–1.99)	$\leq.01$	1.2 (0.6–1.7)	$<.05$
	0.25	0.81 (0.20–1.31)		0.99 (0.40–1.56)		0.9 (0.3–1.2)	
	0.00	2.21 (1.45–2.95)	NS	2.76 (1.84–3.40)	NS	1.8 (1.3–2.6)	NS
	0.10	1.87 (0.66–3.41)		2.20 (0.15–3.97)		1.5 (0.8–2.6)	
B. Acetaminophen	0.00	1.39 (0.41–2.56)	$\leq.01$	1.75 (0.37–3.19)	$\leq.01$	1.2 (0.8–1.8)	$\leq.01$
	1.00	0.63 (—0.21–1.71)		0.61 (—0.67–2.19)		0.7 (0.2–1.4)	
	0.00	1.55 (0.95–2.33)	$\leq.01$	1.80 (1.04–3.08)	$\leq.02$	1.2 (1.0–1.5)	$\leq.01$
	0.50	0.64 (0.07–1.37)		0.89 (—0.01–1.78)		0.7 (0.5–1.1)	
	0.00	1.17 (0.28–2.17)	NS	1.10 (0.02–2.52)	NS	1.1 (0.6–2.1)	NS
	0.25	0.82 (0.03–1.80)		0.91 (—0.23–2.24)		0.8 (0.3–1.4)	
	0.00	1.85 (0.68–2.95)	NS	2.29 (0.76–3.47)	NS	1.6 (0.7–2.6)	NS
	0.10	1.68 (1.00–3.38)		1.93 (0.99–4.27)		1.4 (1.0–2.5)	

[a] Given in 0.10 ml of saline solution.

[b] Mean (range) in eight cats.

[c] Wilcoxon matched-pairs signed-ranks test. NS $= p > .05$.

TABLE II. Effect of Antipyretics Injected into the Lateral Cerebral Ventricle on Normal Body Temperature.

Antipyretic	Dose[a] (mg)	2-hr TRI ($\Delta° \times$ hr)[b]	p[c]	3-hr TRI ($\Delta° \times$ hr)	p	Maximum decrease (°)	p
A. Sodium salicylate	0.00	—0.26 (—1.02–0.63)	NS	—0.41 (—1.45–0.53)	NS	0.4 (0.0–1.0)	NS
	1.00	—0.52 (—1.89–0.08)		—0.79 (—2.18–0.02)		0.6 (0.2–1.2)	
	0.00	—0.01 (—0.61–1.37)	NS	0.08 (—0.61–1.63)	NS	0.4 (0.0–0.8)	NS
	0.50	0.05 (—1.38–1.31)		0.12 (—1.38–1.29)		0.3 (0.0–1.1)	
B. Acetaminophen	0.00	—0.36 (—0.94–0.32)	NS	—0.67 (—1.82–0.30)	NS	0.5 (0.2–0.9)	<.01
	1.00	—0.70 (—1.03–0.22)		—1.08 (—1.73–0.36)		0.7 (0.4–1.1)	
		—		—			
	0.00	0.06 (—0.77–0.76)	≤.05	0.10 (—1.00–1.35)	NS	0.2 (0.0–0.5)	<.05
	0.50	—0.35 (—1.28–0.53)		—0.44 (—1.53–0.93)		0.4 (0.1–0.9)	

[a] Given in 0.10 ml of saline solution.

[b] Mean (range) in eight cats.

[c] Wilcoxon matched-pairs signed-ranks test. NS = $p > .05$.

tically significant antipyresis (Table IB). In the absence of LP (Table IIB) these doses of acetaminophen also caused significantly greater maximum decreases than saline solution, and a significant reduction in 2-hr TRI was obtained after the 0.50 mg dose.

Discussion. The above results support earlier reports (2, 5) that centrally injected sodium salicylate can inhibit the pyrogenic effect of peripherally administered LP. Sodium salicylate injected into the lateral cerebral ventricle was approximately 300 times as potent as when injected iv (3) either in terms of the minimum dose which caused statistically significant antipyresis (0.25 mg intraventricular *vs.* 20 mg/kg iv) or in terms of doses which produced equivalent reductions in TRI. It has been suggested (8) that the difficulty of some workers to obtain antipyretic effects against endogenous pyrogens when the antipyretic was given prior to pyro-

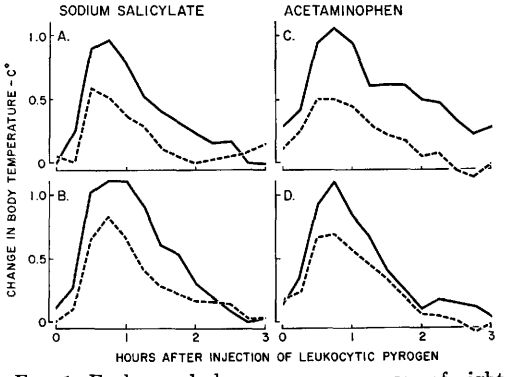

FIG. 1. Each panel shows mean responses of eight cats to iv administration of LP 30 min after intraventricular injection of saline solution (solid lines) or of the antipyretic indicated above (dashed lines). The dose of antipyretic was 1.00 mg in the experiments represented in panels A and C or 0.25 mg in the experiments represented in panels B and D.

gen administration may be the result of using excessive doses of pyrogen. With the possible exception of the doses of LP used in the assay with 0.10 mg sodium salicylate, submaximal doses of LP were given in these experiments in the cat, and there were no particular difficulties in demonstrating antipyretic effects. The lack of any consistent hypothermic effect with salicylate in the cat is also in agreement with results in the rabbit (2, 5). These studies, along with reports of inhibition of fever production by intracerebral administration of bacterial pyrogens when sodium salicylate was given peripherally in cats (9) or monkeys (10), constitute considerable evidence for a central site of antipyretic action of salicylate in a variety of species.

Acetaminophen also acts centrally to inhibit fever. Studies in the cat have previously shown that peripherally or centrally administered acetaminophen inhibits fever production by intraventricular injections of bacterial pyrogens (9, 11, 12). This antipyretic activity of acetaminophen against endotoxin in the cat is most likely related to its ability to inhibit the activity of LP released by endotoxin since acetaminophen, in doses as low as 5 mg/kg iv, effectively antagonized fever production by LP injected iv, while no effect on *in vitro* release of LP from blood leukocytes by endotoxin could be demonstrated (3). The ability of intraventricularly administered acetaminophen to inhibit the pyrogenic effect of LP in the present study further indicates a central site for the interaction between LP and acetaminophen. The antipyretic potency of acetaminophen after intraventricular injection was approximately 40 times the potency after iv injection (3). The hypothermic effect of intraventricular acetaminophen was mild but consistent enough to be statistically significant at doses somewhat lower than those reported by Milton and Wendlandt (12). The antipyretic effect appears to consist of more than just a hypothermic effect because of the greater reduction in temperature obtained after a given dose of acetaminophen in febrile than in afebrile animals and because doses which do not cause hypothermia may still be antipyretic (9).

In previous studies in which the antipyretic effects of sodium salicylate and acetaminophen were examined concurrently (3, 9) acetaminophen was much more effective in reducing fever caused by intraventricularly injected endotoxin and was approximately four times as potent as sodium salicylate in inhibiting the pyrogenic activity of either endotoxin or LP administered iv. These differences in potency probably reflect differing rates of penetration of these antipyretics into the central nervous system (13) since sodium salicylate was not less potent than acetaminophen when both were given intraventricularly.

Summary. Lateral cerebral ventricular administration of sodium salicylate (0.25–1.00 mg) and acetaminophen (0.50–1.00 mg) significantly inhibited production of fever by LP injected iv in the cat. Acetaminophen also caused mild but significant hypothermia in the absence of fever. The ability of these antipyretics to antagonize fever produced by LP, and by agents such as bacterial pyrogens which release LP, is most likely due primarily to a central action to inhibit the effect of LP rather than to a peripheral action to alter LP release from leukocytes or to inhibit entry of LP into the central nervous system.

Note added in proof. Since this paper was submitted for publication, evidence for a central antipyretic action of sodium acetylsalicylate against LP-induced fever in the monkey has been reported by Chai, C. Y., Lin, M. T., Chen, H. I., and Wang, S. C., Neuropharmacology **10**, 715 (1971).

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