J. Pharm. Pharmacol. 1982, 34: 740–741
Communicated May 10, 1982

0022–3573/82/110740–02 $02.50/0

Indirect sympathomimetic effect of some H_2-histamine receptor antagonists in the isolated uterus of the rat

E. RUBIO*, F. J. MORALES-OLIVAS, E. MORCILLO, J. ESPLUGUES, *Departmento de Farmacología, Facultad de Medicina, Avda. Blasco Ibañez, 15, Valencia-10, Spain*

Following the introduction of the first selective antagonist of histamine H_2-receptors, burimamide (Black et al 1972), the drug was shown also to block α-adrenoceptors and to be a potent catecholamine-releaser (Brimblecombe et al 1976).

Metiamide and cimetidine are also potent catecholamine releasers (Brimblecombe et al 1976; Nowak et al 1978). In recent studies characterizing the type of histamine-receptors involved in the inhibitory response to histamine (Goyal & Verma 1981) and clonidine (Rubio et al 1981) in the rat isolated uterus, little attention has been paid to the effects of the H_1 and H_2-histamine receptor antagonists used. In the present study we have evaluated the effects of various selective histamine-receptor blockers on the plateau-contraction induced by K^+-depolarization and its modification after treatment with β-adrenoceptor blockade and catecholamine depletion.

Method

Uterine horns from virgin, oestrogenized (dihydrostilboestrol 5 μg g^{-1} i.p. 24 h before) Wistar rats were mounted in 20 ml water-jacketted organ baths (de Jalon solution, 31 °C, carbogen) and connected to an isotonic transducer (Hewlett Packard). After equilibration for 30 min under a resting tension of 1 g, a submaximal well-maintained (3 h) plateau contraction was obtained by adding KCl 37 mM, and then, a three-points cumulative concentration response curve was obtained for an ethylenediamine derivative with H_1-blocker properties, clemizole (generously supplied by Schering), and for the H_2-blockers metiamide, cimetidine (both kindly suplied by Smith-Kline & French) and ranitidine (A. Gamir, Spain).

In other experimental groups, the uterus was depolarized and then incubated (15 min) with propranolol 0·1 μM or the animals pretreated with reserpine (5 mg kg^{-1} i.p. 24 h before the experiment) or 6-hydroxydopamine (2 × 50 mg kg^{-1} i.p. 96 h before plus 2 × 100 mg kg^{-1} i.p. 24 h before the experiment) to see if any modification appeared in the inhibitory response to the various concentrations of cimetidine used. Additional experiments involved incubating (15 min) with atropine 0·1 μM or methysergide 0·1 μM.

Results and discussion

As shown in Table 1, cimetidine and metiamide, but neither ranitidine nor other antagonists, produced a dose-related inhibition of the K^+-induced tone. No attempt was made to surmount the concentration of the antagonists to see if greater relaxations could be achieved because our aim was to detect if an indirect effect was present in the usual concentration range used as histamine-receptor blockaders.

Pretreatment with either propranolol, reserpine or 6-hydroxydopamine virtually abolished the relaxation induced by cimetidine. In contrast, no attenuation was observed after atropine or methysergide (Table 2).

In conclusion, besides their direct H_2-histamine receptor blocking activity, these substances, with the exception of ranitidine, have the ability to release

* Correspondence.

Table 1. Responses to metiamide, cimetidine, ranitidine and other antagonists in the depolarized uterus of the rat.

		Drug concn (μM)†		
	n*	0·1	1	10
Metiamide	7	−3·55±1·37	−5·73±1·95	− 9·20±2·16
Cimetidine	9	−0·47±0·21	−3·15±1·06	−17·28±6·33
Ranitidine	6	nr‡	nr	nr
Clemizole	8	nr	nr	nr
Propranolol	60	−0·49±0·43	−0·80±0·46	
Atropine	8	+0·25±0·48	(n = 3)	
Methysergide	21	−0·28±0·72		

Responses are mean ± s.e.m. of the percent change of K± induced tone
* No. of experiments.
† Final bath concns.
‡ No response.

Table 2. Modification by various antagonists of the inhibitory response to cimetidine in the depolarized uterus of the rat.

	Cimetidine (μM)		
Pretreatment	0·1	1	10
None	−0·47 ± 0·21 (9)*	−3·15 ± 1·06 (9)	−17·28 ± 6·33 (9)
Propranonol 0·1 μM	+1·01 ± 0·51 (11)	+0·85 ± 0·35 (12)	−0·68 ± 1·51 (6)
Reserpine	+1·22 ± 0·57 (5)	+0·12 ± 0·97 (9)	+1·56 ± 1·67 (9)
6-Hydroxydopamine			−0·19 ± 0·74 (10)
Atropine 0·1 μM		−3·83 ± 1·34 (3)	
Methysergide 0·1 μM		−8·23 ± 4·12 (8)	

Responses are mean ± s.e.m. of the percent change of K^+-induced tone.
* Number of experiments.

catecholamines from adrenergic neural endings in the rat uterus, an organ with a high sensitivity for noradrenaline (Borda et al 1981).

This indirect action should be taken into account when using these drugs as a tool in the pharmacological characterization of the receptors involved in the response to histamine in the isolated uterus of the rat.

REFERENCES

Black, J. W., Duncan, W. A. M., Durant, C. J., Ganellin, C. R., Parsons, E. M. (1972) Nature (London) 236: 885–890

Borda, E., Agostini, M. C., Sterin-Borda, L., Gimeno, M., Gimeno, A. (1981) Eur. J. Pharmacol. 69: 55–62

Brimblecombe, R. W., Duncan, W. A. M., Owen, D. A. A., Parsons, M. E. (1976) Fred. Proc. Fed. Am. Soc. Exp. Biol. 35: 1931–1934

Goyal, R. K., Verma, S. C. (1981) Agents Actions 11: 312–317

Nowak, J. Z., Pilc, A., Mascinski, C. (1978) Eur. J. Pharmacol. 51: 71–75

Rubio, E., Morales-Olivas, F. J., Morcillo, E., Esplugues, J. (1981) IRCS Med. Sci. 9: 804–805

J. Pharm. Pharmacol. 1982, 34: 741–743
Communicated May 6, 1982

0022–3573/82/110741–03 $02.50/0

Pharmacokinetics of theophylline in rats with biliary stasis

RICHARD J. FRUNCILLO*, PAUL DEANGELIS, G. JOHN DIGREGORIO, *Department of Pharmacology, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania 19102, U.S.A.*

Cholestasis in man can be caused by gallstones, tumours of the pancreas or biliary tract, and various drugs (Brooks 1974). The backflow of bile into the liver may produce histological and biochemical abnormalities within the hepatocyte manifested clinically by jaundice and abnormal liver function tests (Brooks 1974). In quantitative electron micoscopy studies, cholestatic rats have demonstrated decreased amounts of hepatic smooth endoplasmic reticulum, the major organelle involved in drug metabolism (Jones et al 1976). Likewise, these same animals were found to have decreased levels of certain drug metabolizing enzymes (Mackinnon & Simon 1975; Drew & Priestly 1976).

Many patients with biliary stasis have concurrent illnesses requiring therapy with several drugs some of which depend primarily on the liver for their metabolic inactivation. Theophylline is such a drug (Piafsky & Ogilvie 1975). In patients with liver dysfunction caused by chronic passive congestion (Piafsky et al 1977) and cirrhosis (Mangione et al 1978), the elimination half-life and clearance of theophylline are significantly prolonged. No information is currently available on the pharmacokinetics of theophylline in patients with abnormal liver function secondary to cholestasis. The purpose of this present study is to investigate the pharmacokinetic parameters of theophylline in rats with extrahepatic cholestasis as a model for the human condition.

Materials and methods

Male Sprague-Dawley rats (220–270 g) were housed one to a cage over corn cob bedding in a well ventilated room (24 ° ± 0·5 °C) with alternate 12 h periods of light and dark. The animals were divided into three groups. The first group consisted of six bile duct-ligated animals fed water and Purina Rodent Chow *ad libitum*. The second group was composed of six sham-operated rats which were pair-fed daily to the bile duct-ligated animals. The third group consisted of three non-operated controls fed *ad libitum*. Double ligation of the common bile duct was performed under sodium pentobarbitone anaesthesia (50 mg kg^{-1}) through a midline excision. Sham animals were anaesthetized similarly but only had their bile ducts exposed before being closed. *Ad lib*-fed control animals were not anaesthetized.

Theophylline kinetics were performed 72 h after the operation under 1·7 g kg^{-1} urethane, an anaesthetic that does not inhibit certain drug metabolic reactions

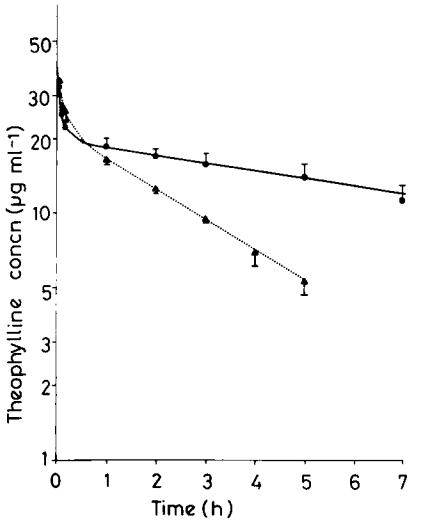

FIG. 1. Plasma concentration of theophylline after 15 mg kg^{-1} i.v. in bile duct ligated rats (●——●) and pair-fed shams (▲ · · · · ▲). Values are mean ± s.e. with n = 6 at each point.

* Correspondence.