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Comparison of the antihistaminic effect of burimamide and mepyramine and their effect on the activity of histamine methyltransferase

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METHYLATION of histamine by histamine methyltransferase (HMT; EC 2.1.1.8) is the predominant mode of inactivation of this amine in most animal species.[1] Recently it was shown that antihistaminic drugs could inhibit or potentiate the activity of this enzyme depending on the concentration of substrate.[2] There was a partial correlation between this effect on the activity of HMT and the antihistaminic activity of these drugs which suggested that the mechanism by which drugs antagonize the physiological effects of histamine may involve an interaction with HMT. This has been further investigated in the guinea pig by comparing the effects of mepyramine, which blocks the effect of histamine on smooth muscle such as that found in the ileum (H_1-receptors[3]), and the effect of burimamide, which blocks the effect of histamine on the atria (H_2-receptors[4]), on the activity of HMT partially purified from the guinea pig ileum, atria, stomach and brain.

Burimamide [*N*-methyl-*N'*-(4-(4-5)-imidazolyl)butyl]thiourea was kindly donated by Dr. J. W. Black (Smith, Kline & French Laboratories, Welwyn Garden City, England). Mepyramine maleate was obtained from May & Baker Ltd. (Dagenham, England). HMT was partially purified[5] from the brain, ileum, atria and the glandular section of the stomach of male albino guinea pigs (400–500 g). The specific activity of the final preparation from all tissues was five times greater than the original supernatant fraction of the homogenate.

HMT activity was assayed by a micromodification[6] of the procedure of Snyder and Axelrod.[7] Endogenous histamine and the activity of histidine decarboxylase were measured by the technique of Taylor and Snyder.[6]

Burimamide can block the effect of histamine on the atrium but is fifty times less potent in blocking the histamine effect on the ileum, whereas mepyramine exerts a potent histamine-blocking effect on the ileum but not on the atrium.[4] If this antihistaminic effect in either tissue involves an effect of these drugs on HMT activity, burimamide should preferentially affect the activity of HMT in the atrium, while mepyramine should affect HMT activity in the ileum and not *vice versa*.

TABLE 1. EFFECT OF MEPYRAMINE AND BURIMAMIDE ON THE ACTIVITY OF HMT *in vivo* AND *in vitro*, AND THE CONCENTRATION OF HISTAMINE IN THE GUINEA PIG BRAIN, ILEUM, ATRIUM AND STOMACH*

	Brain	Ileum	Atrium	Stomach
HMT activity *in vivo*				
K_m	$3{\cdot}3 \times 10^{-5}$M	$3{\cdot}5 \times 10^{-5}$M	$3{\cdot}4 \times 10^{-5}$M	$3{\cdot}3 \times 10^{-5}$M
K_i burimamide	$2{\cdot}8 \times 10^{-4}$M	$2{\cdot}6 \times 10^{-4}$M	$2{\cdot}7 \times 10^{-4}$M	$2{\cdot}4 \times 10^{-4}$M
K_i mepyramine	$2{\cdot}1 \times 10^{-5}$	$2{\cdot}1 \times 10^{-5}$M	$2{\cdot}3 \times 10^{-5}$M	$2{\cdot}2 \times 10^{-5}$M
HMT activity *in vitro* (μmoles/g protein/hr)				
Control	$1{\cdot}05 \pm 0{\cdot}09$	$0{\cdot}85 \pm 0{\cdot}07$	$0{\cdot}33 \pm 0{\cdot}03$	$0{\cdot}95 \pm 0{\cdot}06$
Burimamide (25 mg/kg, i.p. 1 hr)	$0{\cdot}96 \pm 0{\cdot}08$	$0{\cdot}78 \pm 0{\cdot}08$	$0{\cdot}31 \pm 0{\cdot}03$	$0{\cdot}94 \pm 0{\cdot}06$
Mepyramine (25 mg/kg, i.p. 1 hr)	$0{\cdot}98 \pm 0{\cdot}07$	$0{\cdot}81 \pm 0{\cdot}06$	$0{\cdot}38 \pm 0{\cdot}04$	$0{\cdot}98 \pm 0{\cdot}08$
Endogenous histamine (μg/g)				
Control	$0{\cdot}065 \pm 0{\cdot}004$	$5{\cdot}96 \pm 0{\cdot}48$	$5{\cdot}71 \pm 0{\cdot}32$	$12{\cdot}7 \pm 1{\cdot}1$
Burimamide (25 mg/kg, i.p., 1 hr)	$0{\cdot}062 \pm 0{\cdot}005$	$6{\cdot}47 \pm 0{\cdot}51$	$5{\cdot}58 \pm 0{\cdot}30$	$12{\cdot}6 \pm 0{\cdot}9$
Mepyramine (25 mg/kg, i.p., 1 hr)	$0{\cdot}064 \pm 0{\cdot}004$	$6{\cdot}18 \pm 0{\cdot}41$	$5{\cdot}49 \pm 0{\cdot}41$	$13{\cdot}2 \pm 1{\cdot}4$

* Each value is the mean ± S.E.M. of four to six determinations. In no case was the mean of the drug-treated group significantly different ($P < 0{\cdot}05$) from the mean of the control group.

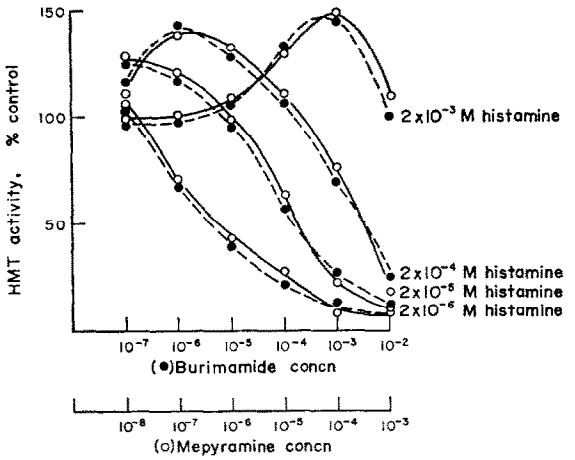

FIG. 1. Effect of mepyramine and burimamide on the activity of histamine methyltransferase (HMT) at various concentrations of histamine. The activity of HMT partially purified from guinea pig ileum was estimated in the presence of increasing concentrations of mepyramine or burimamide while the concentration of the substrate, histamine, was kept at 2×10^{-3} M, 2×10^{-4} M, 2×10^{-5} M or 2×10^{-6} M. Drugs were incubated with the enzyme for 5 min prior to the addition of the methyl donor, *S*-adenosyl-L-methionine (50 μM). Each point is the mean of four determinations. Practically identical results were obtained when the source of HMT was the guinea pig atrium, stomach or brain.

However, it was found that HMT partially purified from brain, ileum, atria and stomach had the same K_m value for histamine and that the K_i value for either drug was practically identical for all tissues studied (Table 1). Moreover, the activity of HMT from all tissues was potentiated to a similar degree at all concentrations of histamine by burimamide and mepyramine (Fig. 1), although mepyramine was 10 times as potent as burimamide. One hour after an intraperitoneal injection of either drug, there was no effect on the activity of HMT *in vivo* or on the concentration of endogenous histamine in the brain, ileum, atria and stomach (Table 1). Thus there was no correlation between the ability of these drugs to block the action of histamine in any tissue and their effect on the activity of HMT.

In other experiments it was found that neither drug interfered with the activity *in vitro* of brain and stomach histidine decarboxylase, and ileum monoamine and diamine oxidase.

Therefore the antihistamine effect of burimamide on H_2-receptors and of mepyramine on H_1-receptors is probably a direct receptor blockade. As any drug that has antihistaminic activity also affects the activity of HMT,[2] there must be structural similarities between the active site of the receptor and the enzyme such as those that occur between the cholinergic receptor and acetylcholinesterase. Interestingly, it was recently found that the cholinergic receptor blocker, atropine, also affected the activity of acetylcholinesterase which, like histamine methyltransferase, may have allosteric properties.[8] The physiological significance of such dual interactions is not known.

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REFERENCES

1. R. W. SCHAYER, *Br. J. Pharmac. Chemother.* **11,** 472 (1956).
2. K. M. TAYLOR and S. H. SNYDER, *Molec. Pharmac.* **8,** 300 (1972).
3. A. S. F. ASH and H. O. SCHILD, *Br. J. Pharmac. Chemother.* **27,** 427 (1966).
4. J. W. BLACK, W. A. M. DUNCAN, C. J. DURANT, C. R. GANELLIN and E. M. PARSONS, *Nature, Lond.* **236,** 385 (1972).
5. D. D. BROWN, R. TOMCHICK and J. AXELROD, *J. biol. Chem.* **234,** 2948 (1959).
6. K. M. TAYLOR and S. H. SNYDER, *J. Neurochem.* **19,** 1343 (1972).
7. S. H. SNYDER and J. AXELROD, *Biochim. biophys. Acta* **111,** 416 (1965).
8. G. KATO, E. TAN and J. YUNG, *Nature New Biol.* **236,** 185 (1972).