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COMMUNICATIONS

Are antihistamines sedative via a blockade of brain H_1 receptors?

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Most antihistamines are known to induce sedative side effects but the mechanism remains unclear (Pollard et al 1973). Such an impairment of central nervous function could possibly be attributed to a blockade of the brain's H_1 receptors, recently shown biochemically (Chang et al 1978; Hill et al 1978; Tran et al 1978). Even if the role of histamine as putative neurotransmitter (Schwartz 1975; Schwartz et al 1976) appears somewhat difficult to evaluate, both the presence of histaminergic fibres innerving the telencephalon via the lateral hypothalamic area (Dropp 1972) and the fact that brain histamine concentration or histamine turnover exhibited circardian variations (Orr & Quay 1975; Friedman & Walker 1968), might suggest a role of histamine on wakefulness and sleep (Verdiere et al 1977).

Recently, a new phenothiazine derivative, mequitazine or (10-[3-quinuclidinylmethyl]-phenothiazine) has been described as a potent H_1 antagonist with few or no sedative side effects on the basis of pharmacological (Rouganne et al 1972; Uzan & Le Fur 1977) and clinical (Gervais et al 1975; Blamoutier 1976; Muler & Blum 1977) data. As [^{3}H]mepyramine has shown to be a selective ligand for H_1 receptors in the brain (Chang et al 1978; Hill et al 1978) and ileum (Hill et al 1977), the affinity of mequitazine for those H_1 receptors in guinea-pigs has been compared with that of classical sedative antihistamines.

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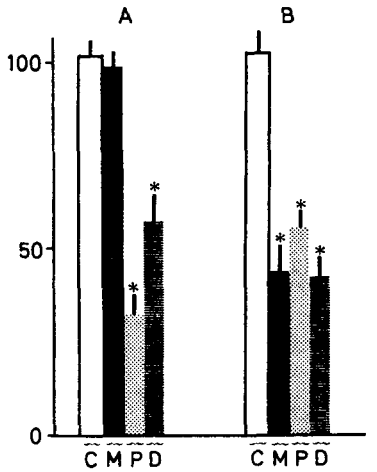

FIG. 1. In vivo inhibition of specific [^{3}H]mepyramine binding (ordinate: %) to guinea-pig brain (A) and ileum (B) H_1 receptors by mequitazine (M), promethazine (P) and (+)-chlorpheniramine (D). Values represent the mean of 5 to 10 guinea-pigs. Each determination (total and nonspecific binding) was in triplicate. The animals were killed 30 min after a single intraperitoneal injection of saline (C) or 5 mg kg^{-1} of drugs. Binding studies were investigated by the methods of Hill et al (1977) for the ileum with slight modifications and of Chang et al (1978) in the brain minus cerebellum on the same animal. * $P < 0.001$.

Male guinea-pigs (300 ± 20 g) and male Sprague-Dawley rats (200 ± 10 g) were used. [^{3}H]Mepyramine (28·5 Ci mmol^{-1}) and [^{3}H]WB 4101 (25·4 Ci mmol^{-1}) were purchased from NEN. The binding of [^{3}H]mepyramine has been investigated in guinea-pig tissues according to Chang et al (1978) in the brain minus cerebellum, and of Hill et al (1977) in the ileum, except that the incubation was stopped by rapid filtration (Whatman GF/B filters) under vacuum followed by four washes with 4 ml of phosphate buffer. Non specific binding was determined by using 2×10^{-6} M of mepyramine.

The binding of the α-noradrenergic antagonist [^{3}H]WB 4101 (2-([2',6'-dimethoxy]-phenoxyethylamino)-methylbenzodioxane) has been investigated in the rat brain according to the method of Greenberg et al (1976). K_i values were obtained by the following formula: $K_i = \frac{I50}{1 + S/K_D}$, where I50 is the concentration of drug required for 50% inhibition of receptor [^{3}H]ligand binding, S is the concentration of [^{3}H]ligand and K_D the dissociation constant.

Scatchard analysis indicates, for both organs, a single component which binds [^{3}H]mepyramine with K_D of 1·6 nmol in ileum and 1 nmol in brain where the respective maximal number of binding sites are 0·08 pmol mg^{-1} protein (ileum) and 0·14 pmol mg^{-1} protein (brain). These results comply with the values in the literature (Chang et al 1978; Hill et al 1977, 1978). A single injection of 5 mg kg^{-1} of mequitazine, promethazine and (+)-chlorpheniramine induces a decrease of 50 to 60% of [^{3}H]mepyramine binding in the ileum (Fig. 1). On the contrary these drugs are not equally effective in the brain. Mequitazine has no effect whereas promethazine and (+)-chlorpheniramine strongly inhibit [^{3}H]mepyramine binding in the brain, promethazine being the most potent. Such a difference

Table 1. In vitro effect of antihistaminic agents on specific [^{3}H]mepyramine binding to guinea-pig brain. Brain homogenates were incubated with 2 nM of [^{3}H]-mepyramine together four to six concentrations of unlabelled drugs under standard assay conditions according to Chang et al (1978) in the brain minus cerebellum. I50 values were determined by log-probit analysis and apparent K_I values calculated from the equation $K_I = \frac{I50}{1 + S/K_D}$.

Drugs	K_I in nM
Mequitazine	280
Promethazine	17
(+)-Chlorpheniramine	12
Cimetidine	> 10 000

between peripheral and central efficacy of mequitazine on H_1 receptors could be explained either by a different affinity of mequitazine for brain and ileum H_1 receptors or by its failure to cross the blood brain barrier. This second hypothesis seems unlikely since previous pharmacokinetic studies with [^{35}S]mequitazine indicated that this compound was able to penetrate into the brain (Uzan et al 1976). Moreover in vitro determinations of K_I values of [^{3}H]mepyramine binding in the brain reveal that mequitazine is 15 to 20 times less potent than (+)-chlorpheniramine and promethazine in the brain (Table 1) whereas mequitazine, promethazine and (+)-chlorpheniramine seem to possess a similar affinity for H_1 ileum receptors since they are equipotent as inhibitors of the contractile response to histamine in vitro and of the bronchospasm in the guinea-pig or the hypotension in the dog induced in vivo by histamine Rouganne et al 1972; Uzan & Le Fur 1977).

These results suggest that mequitazine possesses a greater affinity for peripheral H_1 receptors than for central H_1 receptors, which could explain the absence of sedative side effects. Several authors have attributed neuroleptic-induced sedative effects to a blockade of central α-adrenoceptors (Janssen et al 1965; Peroutka et al 1977). Because of the structural analogy between some neuroleptic and antihistaminic agents, we have compared the effects of mequitazine, promethazine and (+)-chlorpheniramine on central α-adrenoceptors by using the binding of [^{3}H]WB 4101 in rat cortex (Greenberg et al 1976). Mequitazine (K_I = 13 nM) and promethazine (K_I = 7 nM) produce a similar blockade of central α-noradrenoceptors. On the contrary (+)-chlorpheniramine (K_I = 1275 nM) is practically ineffective. Thus, although the possibility of species differences should be noted, the correlation between sedation and blockade of central α-adrenoceptors established for neuroleptics (Peroutka et al 1977) could not be applied to H_1 antagonists. Finally these observations could suggest that the sedative side effects of antihistamines are associated with a blockade of central H_1 receptors.

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