ELSEVIER

European Journal of Pharmacology 315 (1996) R1–R2

ejp

Rapid communication

Inhibition of histamine versus acetylcholine metabolism as a mechanism of tacrine activity

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Received 11 September 1996; accepted 12 September 1996

Abstract

Following tacrine administration i.p. to mice, the histamine *N*-methyltransferase activity of brain homogenates was more potently inhibited than the acetylcholinesterase activity (ID_{50} of 5.3 mg/kg vs. 13.6 mg/kg). The formation of the metabolite, tele-methylhistamine, in brain of mice treated with an histamine H_3 receptor antagonist was abolished by tacrine with an ID_{50} as low as 1.2 ± 0.4 mg/kg. The participation of histamine in the actions of tacrine and the relevance of histamine H_3 receptor antagonists in Alzheimer's disease are suggested.

Keywords: Histamine-*N*-methyl transferase; Acetylcholinesterase; Histamine H_3 receptor antagonist

Tacrine (1,2,3,4-tetrahydro-9-acridinamine), which alleviates Alzheimer's disease symptoms in some patients without causing intolerable side-effects, displays a complex pharmacological profile (Freeman and Dawson, 1991). Although its most generally accepted mechanism of action is protection of endogenous acetylcholine via acetylcholinesterase inhibition, this remains controversial, namely in view of (i) its associated muscarinic antagonist potency; (ii) the failure of acetylcholine receptor agonists or precursors as well as other acetylcholinesterase inhibitors to show significant therapeutic activity (Freeman and Dawson, 1991). Recently tacrine was found to inhibit rather potently histamine-*N*-methyltransferase, the enzyme responsible for histamine metabolism, in vitro and in vivo and to enhance cerebral histamine levels (Cumming et al., 1990; Nishibori et al., 1991). Together with the alleged role of histamine pathways in vigilance and cognitive processes (Schwartz et al., 1991, 1995), this suggests that the activity of tacrine in Alzheimer's disease might be related to inhibition of histamine metabolism.

To investigate this possibility we compared in the same animals receiving tacrine and under parallel ex vivo conditions, the inhibition of cerebral acetylcholinesterase and that of histamine-*N*-methyltransferase. We also assessed the inhibition of histamine metabolism by measuring changes in levels of tele-methylhistamine, the histamine-*N*-methyltransferase product, after histamine release elicited by thioperamide, an H_3 autoreceptor antagonist.

Groups of 5 male Swiss mice (Iffa Credo, 20 g) received tacrine (and eventually 10 mg/kg thioperamide) i.p. and were killed either 30 min later (histamine-*N*-methyltransferase and acetylcholinesterase activities assays) or 45 min later (tele-methylhistamine assays). The cerebral cortex was rapidly homogenized in 20 volumes of phosphate buffer (20 mM, pH 7.8). Histamine-*N*-methyltransferase activity was assayed in the presence of 4 μM histamine and 1.25 μM [^{3}H]*S*-adenosyl methionine (Garbarg et al., 1989) and acetylcholinesterase activity in the presence of 0.2 mM acetylthiocholine and 0.5 mM dithio-bis-nitrobenzoate. Tele-methylhistamine was radioimmunoassayed in 0.4 M $HClO_4$ extracts (Garbarg et al., 1989).

Following tacrine treatment, histamine-*N*-methyltransferase was maximally inhibited by $108 \pm 6\%$ with an ID_{50} of 5.3 ± 0.9 mg/kg whereas corresponding values were $114 \pm 10\%$ and 13.6 ± 3.1 mg/kg for acetylcholinesterase (analysis by an iterative program derived from the Parker and Waud method). The H_3 receptor antagonist-induced increase in tele-methylhistamine was maximally inhibited by $103 \pm 7\%$ with an ID_{50} of 1.2 ± 0.4 mg/kg (Fig. 1). Tele-methylhistamine levels in mice not receiving the H_3 antagonist were also progressively reduced by tacrine treat-

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PII S0014-2999(96)00738-8

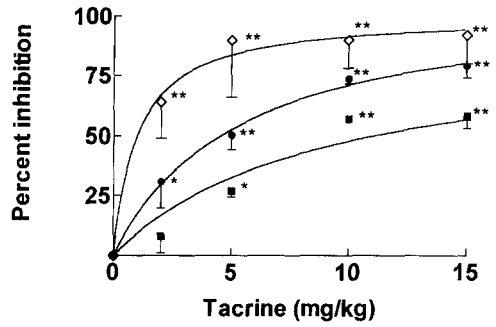

Fig. 1. Dose-dependent inhibition of histamine-*N*-methyltransferase (●) or acetylcholinesterase (■) activities and of H_3 antagonist-induced increase in tele-methylhistamine level (◇) in cerebral cortex of 5 mice receiving tacrine. * $P < 0.05$; ** $P < 0.001$. Basal histamine-*N*-methyltransferase and acetylcholinesterase activities were 7.8 ± 0.3 pmol/g per min and 3.8 ± 0.4 μmol/g per min, respectively. Tele-methylhistamine levels (ng/g) were 78 ± 4 and 122 ± 7 after saline and thioperamide administration, respectively, in non-tacrine-treated mice.

ment with an ID_{50} of 9.0 ± 1.1 mg/kg and a maximal inhibition of $47 \pm 3\%$ (not shown). Doses above 20 mg/kg were toxic.

Hence tacrine was more potent to inhibit histamine-*N*-methyltransferase than acetylcholinesterase in vivo although the ID_{50} values in the ex vivo test should be considered only relatively, rather than as absolute values, in view of the changes in reversible inhibitory patterns of the enzymes related to the necessary dilution of cerebral extracts for assays (Thomsen et al., 1989). In agreement, the K_i values of tacrine were 35 nM against histamine-*N*-methyltransferase (Cumming et al., 1990) and 90–630 nM against acetylcholinesterase (Freeman and Dawson, 1991). In addition the ID_{50} of tacrine (1.2 mg/kg) for inhibition of neosynthetized histamine metabolism was one of the lowest doses among those required for any behavioral or biochemical effect.

Since enhancement of histamine release by H_3 autoreceptor antagonists facilitates learning in aged rats (Meguro et al., 1995) and performance in attention tests (J. Muir, personal observation), our data support a role of endogenous histamine in the cognitive effects of tacrine. Furthermore, they suggest that the association of tacrine and an H_3 antagonist, well tolerated in mice, might represent a novel therapeutic approach in Alzheimer's disease.

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