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REFERENCES

Amar, A., Sanyal, A. K. (1981) Psychopharmacology 73: 157–160

Borella, L. E., Seethaler, K., Lippmann, W. (1979) Arzneimittel-Forsch/Drug Res. 29 (1): 793–798

Burnett, A. R., Thomson, R. H. (1968) J. Chem. Soc. Sec. C: 850–853

Chunekar, K. C., Pandey, G. S. (1969) in: Bhavprakash Nighantu of Bhavamishra (Indian Materia Medica) 4th ed., Chaukhamba Vidya Bhawan, Varanasi, p. 549

Debnath, P. K., Gode, K. D., Govinda Das, D., Sanyal, A. K. (1974) Br. J. Pharmacol. 51: 213–216

Eagleton, G. B., Watt, J. (1965) J. Pathol. Bacteriol. 90: 679–682

Eagleton, G. B., Watt, J. (1967) Ibid. 93: 694–696

Gallagher, G. T., Szabo, S. (1984) Digestion 29: 73–84

Goel, R. K., Chakrabarti, A., Sanyal, A. K. (1985) Planta Medica 2. 85–88

Kirtikar, K. R., Basu, B. D. (1944) Indian Medicinal Plants Vol. III: 1924–1926

Pandey, B. L., Goel, R. K., Pathnak, N. K. R., Biswas, M., Das, P. K. (1982) Ind. J. Med. Res. 76 (Suppl): 89–94

Sandermann, W., Simatupang, M. H. (1968) Bull. Nat. Inst. Sci. India 37: 158–160

Sanyal, A. K., Debnath, P. K., Bhattacharya, S. K., Gode, K. D. (1971) in: C. J. Pfeiffer (ed.) Peptic ulcer, Munksgaard, Copenhagen, pp 312–318

Sanyal, A. K., Pandey, B. L., Goel, R. K. (1982) J. Ethnopharmacol. 5: 79–89

Sanyal, A. K., Mitra, P. K., Goel, R. K. (1983) Ind. J. Exp. Biol. 21: 78–80

Singh, B., Chunekar, K. C. (1972) Glossary of vegetable drugs in Brihattaray, Ist ed., Chaukhamba Sanskrit Series Office, Varanasi, pp 392–393

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Anticholinergic activity of the dopamine receptor agonist, TL-68 (*N*,*N*-dipropyl-2-aminotetralin)

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The anticholinergic properties of a dopamine receptor agonist, a non-hydroxylated derivative of *N*,*N*-dipropylaminotetralin (TL-68), were evaluated using the guinea-pig isolated tracheal strip and rat phrenic nerve-diaphragm preparations. TL-68 competitively antagonized carbachol-induced contractions in guinea-pig trachea with a pA_2 value of 5·88 ± 0·05. In the rat phrenic nerve-diaphragm preparation, TL-68 was found to be inactive in blocking nicotinic cholinergic receptors.

A dopamine receptor agonist, a non-hydroxylated derivative of *N*,*N*-dipropyl-2-aminotetralin (TL-68), produces central dopaminergic activity including emesis in dogs, inhibition of prolactin secretion in rats and contralateral rotation in unilaterally substantia nigra lesioned rats (Rusterholz et al 1979). The peripheral dopaminergic action of TL-68 was evaluated in cat hearts both in-vivo and in-vitro (Ilhan et al 1984).

Our preliminary experiments showed that TL-68 produced inhibition of twitch responses in transmurally stimulated guinea-pig ileum which was not antagonized by phentolamine, haloperidol or naloxone. These results led us to think about the postsynaptic anticholinergic action rather than the presynaptic inhibitory action of TL-68. The aim of this study was to get insight into the possible antimuscarinic and antinicotinic actions of TL-68 by using guinea-pig isolated trachea and rat phrenic nerve-diaphragm preparations.

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Materials and methods

Male guinea-pigs (300–500 g) were killed by a blow to the head. The excised trachea was cleaned of extraneous tissue and cut in a spiral fashion as described by Constantine (1965). The spiral was suspended in an organ bath (10 mL) containing Krebs-Henseleit solution and 2 g of resting tension was applied to the preparation.

The phrenic nerve-diaphragm preparation was prepared according to Bülbring (1946) from male rats (150–300 g). The left hemidiaphragms were suspended under 1 g of resting tension in 20 mL of Krebs-Henseleit solution. A bipolar platinum electrode was used for the phrenic nerve stimulation (indirect stimulation). The nerve was stimulated at a frequency of 0·05 Hz with supramaximal rectangular pulses of 0·1 ms duration. For direct stimulation of the diaphragm, a platinum electrode was attached to the muscle along its intercostal margin. An indifferent platinum electrode was immersed into the solution and supramaximal stimuli of 2 ms duration were applied at 0·05 Hz. The direct and indirect stimulations of the muscle were alternated at an interval of 10 s.

The composition of the Krebs-Henseleit solution was (mM): NaCl 118·4, KCl 4·69, $MgSO_4$ 1·18, $CaCl_2$ 2·5, KH_2PO_4 1·17, $NaHCO_3$ 25·0, glucose 11·1. The solution was maintained at 33 °C and bubbled with a mixture of 95% O_2–5% CO_2.

Isometric contractions of the tracheal strip and the diaphragm were recorded on a polygraph via a Grass FT.03 force displacement transducer.

In the guinea-pig trachea, concentration-response curves were obtained with stepwise cumulative addition of carbachol as an agonist, the concentration of which was increased 10-fold in the bathing medium at each step. Each addition was made only after the response to the previous concentration had attained a maximal and steady level. The tissues were then washed until the responses returned to control level then antagonists (TL-68 or atropine) were added and concentration-response curves to carbachol were reobtained 30 min later.

Experiments were conducted using three effective concentrations of antagonists in each experiment. Dose-ratios for antagonist-induced shifts in the concentration-response curves were estimated by calculating the carbachol concentration producing 50% of the maximum contraction in the absence and presence of antagonist. Schild plots were constructed by the method of Arunlakshana & Schild (1959) and pA_2 values were determined from least-squares estimates of the resultant regression lines.

Results were expressed as mean ± s.e.m. of the number (n) of experiments with their 95% confidence intervals which were determined by probit analysis (Goldstein 1964).

Drugs used were: TL-68 hydrochloride (synthesized in The University of Iowa, USA), atropine sulphate (Merck), carbachol hydrochloride and neostigmine bromide (Sigma).

Results and discussion

At the concentrations tested, TL-68 did not produce contractions in the guinea-pig tracheal strip, but caused parallel displacement to the right of the carbachol concentration-response curve without reducing the maximum response, thus suggesting competitive antagonism at muscarinic cholinergic receptors. Also, the Schild plot regression was linear and the slope was not significantly different from unity ($m = -1{\cdot}11 \pm 0{\cdot}05$ (1·0–1·22)); the pA_2 value of TL-68 was $5{\cdot}88 \pm 0{\cdot}05$ (5·77–5·99) ($n = 11$). The pA_2 value of atropine was found to be $9{\cdot}20 \pm 0{\cdot}07$ (9·00–9·40) ($n = 6$), and the slope of the Schild plot ($m = -1{\cdot}16 \pm 0{\cdot}07$ (0·96–1·36)) was not significantly different from unity.

In the phrenic nerve-diaphragm preparation, TL-68 was found to be inactive at concentrations lower than 1×10^{-4} M. At this concentration, it produced $16{\cdot}0 \pm 4{\cdot}2$ (−2·0–34·6)% ($n = 4$) inhibition in the twitch response to direct stimulation within a 15 min observation period without any change in the indirect response. The highest concentration tested (1×10^{-3} M) abolished responses to both direct and indirect stimulation. This inhibition is not mediated with the blockade of nicotinic cholinergic receptors since inhibition of twitch responses to indirect stimulation was not reversed by neostigmine (1×10^{-4} M) and twitch responses to direct stimulation were also abolished.

At the concentration range used in this study to produce antimuscarinic action, TL-68 is expected to act as a dopamine agonist. If we consider the results of our previous work (Ilhan et al 1984), TL-68 caused about 90% inhibition of the positive chronotropic response in transmurally stimulated cat heart via the stimulation of dopamine receptors at a concentration of 10^{-6} M which is close to the K_B value related to antimuscarinic action of TL-68.

Present treatment of Parkinson's disease is aimed at restoring the cholinergic-dopaminergic balance in the basal ganglia either by supressing muscarinic, cholinergic activity or by enhancing dopaminergic activity. Dopamine receptor agonists may have an advantage if they possess certain additional antimuscarinic properties, leading to more beneficial and less adverse reactions. As far as we know, none of the agents presently used produce both effects simultaneously. TL-68, with its dopamine receptor agonistic and antimuscarinic action, appears to be a particularly interesting drug in this context.

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REFERENCES

Arunlakshana, O., Schild, H. O. (1959) Br. J. Pharmacol. 14: 48–58

Bülbring, E. (1946) Br. J. Pharmacol. Chemother. 1: 38–61

Constantine, J. W. (1965) J. Pharm. Pharmacol. 17: 384–385

Goldstein, A. (1964) Biostatistics. An Introductory Text. Macmillan Publishing Co., New York

Ilhan, M., Long, J. P., Cannon, J. G. (1984) Arch. Int. Pharmacodyn. Ther. 271: 213–219

Rusterholz, D. B., Long, J. P., Flynn, J. R., Cannon, J. G., Lee, T., Pease, J. P., Clemens, J. A., Wong, D. T., Bymaster, F. P. (1979) Eur. J. Pharmacol. 55: 73–82