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Some autonomic blocking properties of zetidoline (DL 308-IT), a novel potential anti-psychotic drug

PAUL FOSBRAEY, MICHAEL F. HIRD, E. STEWART JOHNSON*, *Department of Pharmacology, King's College, Strand, London WC2R 2LS, U.K.*

Zetidoline [DL 308-IT (1-(3-chlorophenyl)-3-[-2-(3,3-dimethyl-1-azetidinyl ethyl]imidazolidin-2-one hydrochloride)] is a novel centrally acting dopamine antagonist, which inhibits apomorphine-induced emesis and stereotypy in the dog, amphetamine stereotypy in the rat, prevents conditioned avoidance responses and increases the turnover of dopamine in rat brain (see Szabadi et al 1980; Barone et al 1982). In healthy volunteers both DL 308-IT and thioridazine displayed sedative properties, caused miosis, hypotension and a decrease in salivation although in equisedative doses DL 308-IT had a smaller influence on autonomic functions than thioridazine (Szabadi et al 1980). Szabadi et al (1980) considered that DL 308-IT (10, 20 mg) caused miosis possibly through an α-adrenoceptor antagonist action although with the smaller of the two doses used they noted an increase in sweating and heart rate which they considered to be a sympathomimetic action of the drug. The decrease in salivation was considered to indicate an anti-acetylcholine effect. It was of interest therefore to identify the peripheral autonomic blocking properties of the new drug on isolated organ preparations in vitro.

Cumulative dose-contractile response curves were made for phenylephrine on the rabbit and guinea-pig aortic spiral preparations and repeated after 30 min incubation with different concentrations of DL 308-IT (1, 10, 40 and 100 μM).

On the rabbit aorta, increasing concentrations of DL 308-IT displaced the log dose-response line of phenylephrine to the right in a parallel manner indicating competitive antagonism of postsynaptic α_1-adrenoceptors. The antagonism was quantified by the method of Arunlakshana & Schild (1959) to give a pA_2 value of 5·99 (slope function −0·93; pA_2–pA_{10} 1·02). Similar results were obtained for DL 308 IT against phenylephrine on the guinea-pig aorta (pA_2 5·82; slope function −1·11; pA_2–pA_{10} 0·85; Fig. 1).

Dose-response curves to the cardioaccelerator effect of isoprenaline were constructed on guinea-pig isolated spontaneously-beating atria in the absence and presence of DL 308-IT (100 μM). DL 308-IT did not antagonize this effect of isoprenaline suggesting that the drug has no affinity for β_1-adrenoceptors. Cumulative dose-response curves to the relaxant effect of isoprenaline on the inherent tone of the guinea-pig isolated tracheal spiral preparation were similarly unaffected by DL 308-IT.

On the longitudinal muscle of the guinea-pig isolated ileum dose-contractile response curves to histamine were displaced to the right by increasing concentrations of DL 308-IT (1, 2, 4 and 10 μM). DL 308-IT appeared to be a weak competitive antagonist of histamine H_1-receptors on this preparation (pA_2 5·6; slope function −0·92; pA_2–pA_{10} 1·03). It has previously been reported that the contractile responses of the guinea-pig ileum to acetylcholine were antagonized in a non-competitive manner by DL 308-IT (Fosbraey et al 1980) in concentrations greater than 1 μM.

The drug proved to be a powerful antagonist of the morphine-induced inhibition of the twitch response of the guinea-pig ileum to transmural electrical stimulation (0·2 Hz; 0·5 ms; 7–8 V). The antagonism did not appear to be competitive despite an apparent parallel displacement of log dose-response curves with concentrations less than 8 μM (Fig. 2). This property of DL 308-IT was also shared by metoclopramide (Fosbraey et al 1980).

DL 308-IT in concentrations of 0·1–1·0 μM potentiated the twitch response of the guinea-pig ileum to transmural electrical stimulation, an effect that has

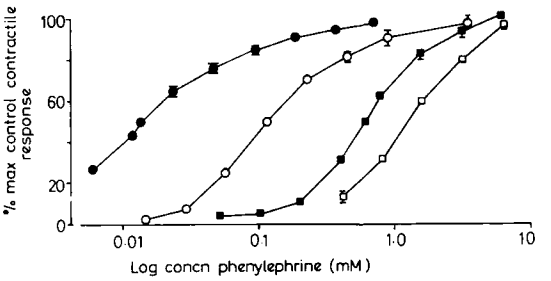

FIG. 1. Effect of increasing concentrations of DL 308-IT on the contractile responses of the guinea-pig aortic spiral preparation to phenylephrine. The results are expressed as mean % maximal contraction in the absence (●) and presence of the antagonist (○ = 10 μM, n = 7; ■ = 40 μM, n = 4; □ = 100 μM, n = 5). Vertical bars indicate s.e.m. except where the error falls within the bounds of the symbol.

* Correspondence.

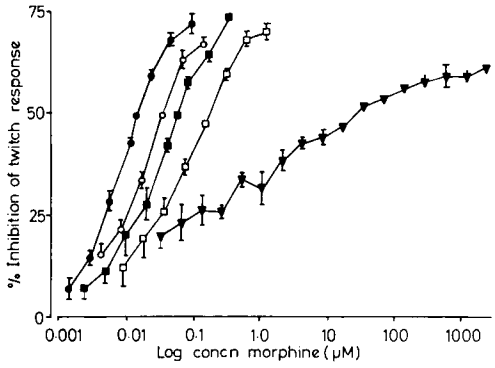

FIG. 2. Effect of increasing concentrations of DL 308-IT on the inhibition of electrically-evoked twitch responses of the guinea-pig ileum caused by morphine. The morphine dose-response curves are shown in the absence (●) and presence of DL 308-IT (○ = 1 μM; ■ = 2 μM; □ = 4 μM; ▼ = 8 μM; n = 6–9). Vertical bars indicate s.e.m. except where error falls within the bounds of the symbol.

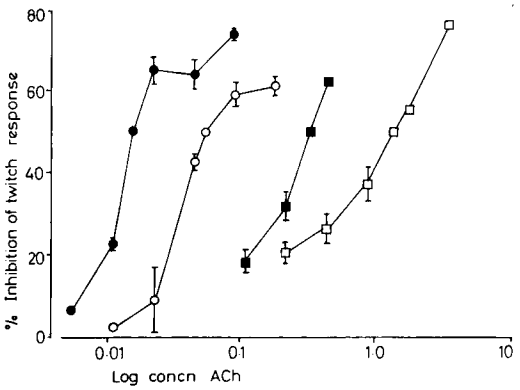

FIG. 3. Effect of increasing concentrations of DL 308-IT on the inhibition of the first post-acetylcholine twitch height to added ACh. The ACh dose-response curves are shown in the absence (●) and presence of DL 308-IT (○ = 1 μM: ■ = 4 μM: □ = 10 μM). Each point is the mean of 4 values ± s.e.m.

been provisionally attributed to selective presynaptic cholinoceptor antagonism (Fosbraey et al 1980). Twitch responses of the guinea-pig ileum when interrupted by the addition of ACh to the bathing medium for 30 s are inhibited for the 10 minute period following the removal of the acetylcholine (Fosbraey & Johnson 1978, 1980). This inhibitory response has been attributed to the activation of presynaptic muscarinic cholinoceptors (Fosbraey & Johnson 1980a). DL 308-IT (1, 4 and 10 μM) displaced the log dose-inhibitory response curves to acetylcholine in a parallel manner to the right of the control (Fig. 3) and the Arunlakshana & Schild plot gave a pA_2 value of 6·75 (slope function = 0·98; pA_2–pA_{10} 0·98). By comparison, the pA_2 value for metoclopramide against ACh-inhibition of twitch was 5·1.

Thus the ability of DL 308-IT to increase sweating in healthy volunteers taking the 10 mg, but not the 20 mg, dose might possibly be attributable to the selective presynaptic cholinoceptor antagonist, rather than to a sympathomimetic, action of the drug. This might also contribute to the pupillary constriction seen in man, although Szabadi et al (1981) have presented evidence that a single 10 mg oral dose of DL 308-IT can block α-adrenoceptors. Similarly the presynaptic cholinoceptor blocking action of metoclopramide would be sufficient to account for the ability of this molecule to increase gastrointestinal motility.

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