Potentiation of Ocular Response to Adrenaline by 3,3-Dimethyl-1-[3-Methylaminopropyl]-1-Phenylphthalan (Lu 3-010) and a Thiophthalan Analogue (Lu 5-003): Blockers of Catecholamine Uptake

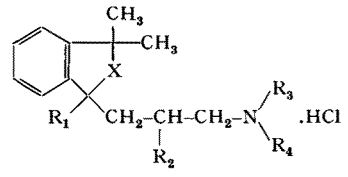
The role of sympathetic nerve activity and adrenergic amines in ocular responses has been the subject of various investigations. Denervation of the ocular tissue surgically[1-3] or pharmacologically[4] results in hypersensitivity of the rabbit eye to the catecholamine-induced[1-3] or endogenously-mediated[4] outflow of aqueous humor. Administration of an agent which causes blockade of uptake of catecholamines into the postganglionic sympathetic neurons results in potentiation of the ocular response[5,6]. Blockade of the catecholamine uptake process, which is at the level of the cell membrane, leads to higher concentrations of catecholamines at the receptor sites since the major mechanism of inactivation is through uptake into storage sites of sympathetic nerve endings[7-9].

The compound 3,3-dimethyl-1-[3-methylaminopropyl]-1-phenylphthalan (Lu 3-010) has been shown to be a potent inhibitor of the catecholamine uptake mechanism[10,11]. Lu 3-010 and various structurally-related compounds lack or have little of an undesirable property, i.e. anticholinergic activity[12,13]. The effects of Lu 3-010 and various structurally-related compounds (Figure 1) on the ocular response to adrenaline were determined and are the subject of this report.

Method. The pupil diameters of both eyes of adult female rabbits (2.5–3.0 kg) were measured under artificial illumination (6V–15W microscopic lamp placed 3″ from the eye) with a transparent plastic millimeter ruler. Student's *t*-test was used in the evaluation of the data.

Results. The effects of Lu 3-010 and various analogues on adrenaline-induced mydriasis were studied. 50 µl of an aqueous solution of the test compound were instilled into one eye, the contralateral eye serving as a control. 5 h later the pupil diameters were again measured following which 50 µl of a 0.5% solution (expressed as free base) of 1-adrenaline bitartrate (Sigma Chemical Co.) in physiological saline was instilled into each eye and the pupil sizes measured 30 min later. 3 rabbits were utilized for each compound studied. Adrenaline at 0.5% caused no increase in pupil size. Lu 3-010 and Lu 5-003 potentiated the action of adrenaline causing an increase in pupil diameter of greater than 3 mm at 0.1%, but not at 0.05% (Table). Neither of the compounds alone at 0.1% caused any changes under these conditions. None of the other structurally-related compounds examined caused an increase in pupil diameter of greater than 1 mm even at 0.25%. Lu 3-010 and Lu 5-003 were similar in activity to protriptyline, a blocker of catecholamine uptake[13], which had been shown previously to exhibit the potentiating activity[6].

The effects on the potentiating activity caused by varying the time of administration of Lu 3-010, Lu 5-003 and



	X	R_1	R_2	R_3	R_4
Lu 3-010	O		H	CH_3	H
Lu 5-003	S		H	CH_3	H
Lu 3-049	CH_2		H	CH_3	H
Lu 3-009	O		H	CH_3	CH_3
Lu 4-074	S		H	CH_3	CH_3
Lu 4-004	O		H	H	H
Lu 3-048	O		CH_3	CH_3	CH_3
Lu 4-012	O	CN	H	CH_3	H
Lu 3-092	O	CN	H	CH_3	CH_3

Fig. 1. Structures of compounds

Effects of Lu 3-010 and structurally-related compounds on potentiation of the ocular response to adrenaline

Compound	Dose (% solution)	Δ Pupil diameter (mm)
Lu 3-010	0.1	4
	0.05	0.6
Lu 5-003	0.1	3.9
	0.05	1.1
Lu 3-049	0.25	0
Lu 3-009	0.25	1.0
Lu 4-074	0.25	0.8
Lu 4-004	0.25	0.8
Lu 3-048	0.25	0
Lu 4-012	0.25	0.8
Lu 3-092	0.25	0.3
Protriptyline	0.1	3.4
	0.05	2

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protriptyline prior to the application of the adrenaline were determined. 5 rabbits were used for each determination. The dose of adrenaline employed (50 µl, 1%) had no effect on pupil diameter. Similar potentiating activities were obtained at each of the different time periods whether the compound was administered 5 or 30 min before the adrenaline (Figure 2). The only exception was with protriptyline, at 3 h, where potentiation was observed when the time interval between treatments was 5, but not 30 min.

The compounds differed in activity when each was administered simultaneously with the adrenaline. Although each exhibited a similar activity 0.5 h after treatment, Lu 3-010 had a more pronounced and longer duration of action than Lu 5-003 since Lu 3-010 caused a greater potentiation at both 1 and 2 h. Lu 3-010 and protriptyline were similar in activity. In a comparison of the results obtained showing the activities of the compounds when each was applied separately from adrenaline it appears that Lu 3-010 and Lu 5-003 were similar whereas protriptyline tended to be more active than either.

For each individual compound a comparison of the combined treatment versus a separate treatment reveals that the potentiating activity was similar after each time period with Lu 3-010, similar or less with Lu 5-003 and, in general, was lower at all time periods with protriptyline.

In order to determine the effect of an α-adrenergic receptor antagonist on the potentiating activity of the 3 compounds, phenoxybenzamine (5 mg/kg, i.v.) was given 1 h prior to 50 µl of a 0.1% solution of each. Adrenaline (50 µl of a 1% solution) was administered 30 min later and after 1 h the pupil diameter was measured; 5 rabbits were used for each treatment. The changes in pupil diameter for Lu 3-010, Lu 5-003 and protriptyline were 5.2 ± 0.3, 3.4 ± 0.7 and 4.8 ± 0.4 mm, respectively. After pretreatment with phenoxybenzamine these values were depressed to 0.7 ± 0.3, 0.5 ± 0.3 and 0.7 ± 0.3 mm, respectively. Thus, phenoxybenzamine prevented the potentiating activity of each of the compounds.

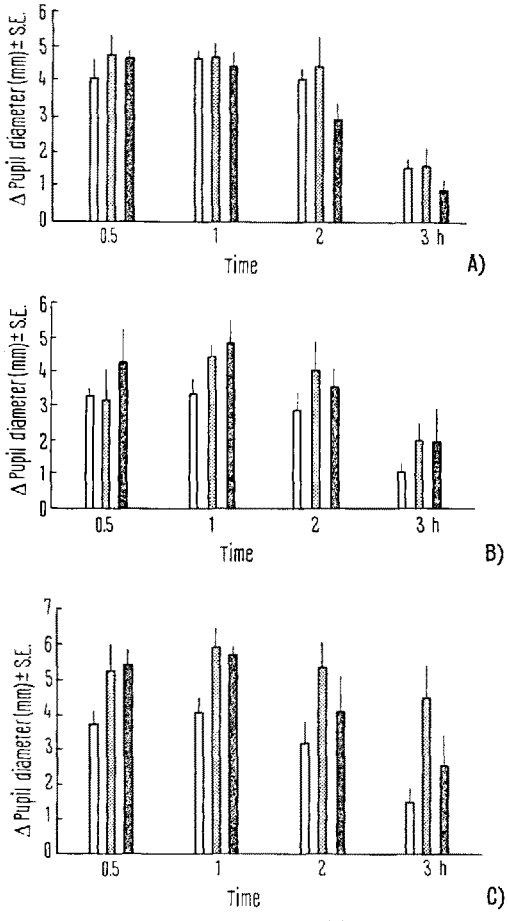

Fig. 2. Effect of time of pretreatment with compounds on pupil response to adrenaline. Compound (50 µl, 0.1%) was applied topically at 0 (⊓), 5 (⊟) or 30 (|) min before adrenaline (50 µl, 1%); changes in pupil diameter were determined after the designated times. A) Lu 3-010. B) Lu 5-003. C) Protriptyline.

Discussion. The present studies indicate that Lu 3-010 and Lu 5-003 potentiate the ocular response to adrenaline. With respect to duration of action in the combined treatment with adrenaline, Lu 3-010 is similar in activity to protriptyline and more active than Lu 5-003. In the separate applications Lu 3-010 and Lu 5-003 are similar while protriptyline tends to be the most active.

The potentiation of the ocular response to adrenaline by Lu 3-010 and Lu 5-003 is probably due to their known ability[10,13] to block the catecholamine uptake mechanism. The findings that the potentiation of the ocular response by Lu 3-010 or Lu 5-003 is blocked by phenoxybenzamine, an α-adrenergic receptor antagonist, is in accord with this suggestion. The results obtained with protriptyline in this respect are in accord with those reported by others[6]. The potentiation of the ocular response is consistent with the potentiation of other activities of catecholamines[14,15] by agents which prevent their uptake. The differences observed in the potentiating activity of the various compounds examined in the present studies could be due to such factors as differences in potency and in duration of action of the compounds with respect to their ability to cause blockade of the uptake mechanism.

The results obtained with phenoxybenzamine also indicate that the ocular responses observed with Lu 3-010 and Lu 5-003 are not due to an anticholinergic effect. In support of this conclusion are the reports that Lu 3-010 lacks[12] and Lu 5-003 is essentially devoid of[13] this activity.

Catecholamines applied topically to normal and glaucomatous eyes of humans have been demonstrated to reduce intraocular pressure[16]. Lu 3-010 and Lu 5-003 may thus be of value in the treatment of glaucoma.

Résumé. Concernant la durée de l'effet du traitement, le composé Lu 3-010 en combinaison avec l'adrenaline est semblable à la protriptyline, et il est plus actif que Lu 5-003 en ce qui concerne la potentiation de la reaction oculaire provoquée par l'adrenaline. Administrés séparement, les composés Lu 3-010 et Lu 5-003 ont des effets semblables, tandis que la protriptyline est le composé le plus actif. L'accroissement de l'efficacité de ces composés résulte probablement de leur abilité à bloquer le mécanisme de l'incorporation de la catecholamine.

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