Effect of Lidoflazine on Norepinephrine, Angiotensin and Serotonin Responses in Isolated Smooth Muscle Preparations

Lidoflazine (1-[4,4-di-(4-fluorophenyl)-butyl]-4-(2,6-dimethyl-(anilinocarbonyl)-methyl]-piperazine) has been described as a long-lasting coronary vasodilator agent by SCHAPER et al.[1,2]. Recently GODFRAIND et al.[3] showed that lidoflazine has an antagonistic action to angiotensin in the isolated longitudinal muscle of the guinea-pig ileum. These authors have claimed that this antagonism is not competitive but highly specific for angiotensin.

We undertook this study to investigate the effect of lidoflazine on the contractile responses produced by norepinephrine, angiotensin and serotonin in the isolated rabbit aortic strip and isolated stomach fundus of the rat.

Spirally cut rabbit aortic strips were prepared according to FURCHGOTT and BHADRAKOM[4]. They were mounted in a 25 ml volume isolated muscle bath in Krebs solution at 37 °C and aerated with oxygen. An isotonic lever exerted a tension of 0.4 g on the strip and was kept constant in all experiments. Drugs added to the bath were expressed as % of the maximal responses of the strip which can be determined by adding an excess of the myotropic agent.

Isolated stomach fundus strip of the rat was prepared according to VANE[5]. Strip was suspended in a 25 ml volume isolated organ bath containing regular Tyrode solution heated 37 °C and aerated by air. The contractions were recorded isotonically on a smoked drum by a frontal lever.

Statistical analysis of the results were carried out using Student's *t*-test. Stock solutions of lidoflazine were prepared from crystalline base by dissolving in distilled water and glacial acetic acid[2].

Lidoflazine itself neither relaxed nor contracted the isolated rabbit aortic strip at the concentration range of 1–10 μg/ml. At the concentration of 1–5 μg/ml lidoflazine did not change the responses to norepinephrine. With 10 μg/ml concentrations it inhibited non-significantly the responses to norepinephrine. The % of maximal response of the intact strip to norepinephrine was 73.8 ± 5.7 ($n = 9$), while it changed to 64.9 ± 2.0 ($n = 9$) in the presence of lidoflazine at 10 μg/ml concentration ($p > 0.10$).

The % response caused by 1 ng/ml of angiotensin was 18.8 ± 1.2 ($n = 5$). When the concentration increased to 5 ng/ml, angiotensin caused a response which was 79.6 ± 2.4 ($n = 5$) % of the maximal. In the presence of lidoflazine (10 μg/ml), the relative response to angiotensin was 10.0 ± 1.1 ($n = 6$) for the concentration of 1 ng/ml and 74.5 ± 4.0 ($n = 5$) for 5 ng/ml.

The results in the isolated rabbit aortic strip for serotonin are summarized in the Table. In contrast to norepinephrine and angiotensin, the action of serotonin was significantly antagonized by lidoflazine at very low concentration. The necessary time of contact with lidoflazine was 3 min. The effect of lidoflazine persisted 2 h in spite of washing out several times with normal Tyrode solution. A similar observation was made in the isolated stomach fundus strip of the rat. In one experiment with this preparation, 4 ng/ml serotonin caused a contraction of 72.0 ± 3.9 mm ($n = 5$). However, in the presence of 1 μg/ml lidoflazine, the same concentration of serotonin produced 11.0 ± 0.7 mm ($n = 5$) response, and 12 ng/ml serotonin caused 41.6 ± 1.1 mm ($n = 5$) response; but 160 ng/ml serotonin produced 75.0 ± 5.0 mm ($n = 4$) which was almost equal to the control response to serotonin.

All these results indicate that lidoflazine has no antagonistic action to norepinephrine and angiotensin in the isolated rabbit aortic strip. However, it caused a significant inhibition of the action of serotonin in both isolated rabbit aorta and isolated stomach fundus strip of the rat. This inhibitory effect was observed after 3 min contact with aortic strip and 5–10 min contact with the stomach strip. However this effect was observed after 60 min contact of lidoflazine with the isolated longitudinal muscle of the guinea-pig ileum against angiotensin according to GODFRAIND et al.[3]. We have some data indicating that 45 min contact is necessary to block serotonin action in the isolated cat tracheal muscle (unpublished observation). We could not obtain an inhibitory action of lidoflazine on the norepinephrine and angiotensin responses even after 60 min contact with the strips at concentrations of 1–2 μg/ml which can block the action of serotonin. We did not use concentrations of lidoflazine higher than 10 μg/ml, to avoid its direct relaxant effect on the smooth muscle.

These results show that lidoflazine has a selective inhibitory action on the responses to serotonin in both isolated rabbit aortic strip and rat stomach fundus strip. This effect is dose dependent suggesting a competitive antagonism. However this consideration is still under investigation[6].

Serotonin (ng/ml)	% of maximal contraction mean ± S.E.		
	Without lidoflazine	With lidoflazine	
		1 μg/ml	2 μg/ml
40	19.0 ± 2.0 ($n = 12$)	10.0 ± 0.8 ($n = 6$)	4.6 ± 2.5 ($n = 6$)
80	34.0 ± 2.3 ($n = 11$)	16.2 ± 1.2 ($n = 5$)	7.8 ± 1.8 ($n = 5$)
120	45.6 ± 5.5 ($n = 5$)	28.3 ± 3.0 ($n = 6$)	–
160	52.0 ± 4.9 ($n = 7$)	–	19.5 ± 2.0 ($n = 6$)
200	57.0 ± 7.0 ($n = 7$)	41.6 ± 4.8 ($n = 5$)	–
240	59.7 ± 1.4 ($n = 4$)	–	–
320	59.0 ± 4.3 ($n = 6$)	53.8 ± 2.2 ($n = 4$)	27.3 ± 2.4 ($n = 6$)
640	–	–	47.2 ± 4.5 ($n = 5$)

Résumé. Les effets de la lidoflazine ont été étudiés sur les bandelettes aortiques isolées du lapin et les bandelettes gastriques isolées du rat. La lidoflazine antagonise significativement la sérotonine sur ces 2 préparations sans altérer leurs réponses à l'angiotensine et à la noradrénaline.

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