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Effect of some receptor antagonists on fenfluramine-induced glucose uptake into the isolated rat hemidiaphragm

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We have shown (Kirby, 1974; Kirby & Turner, 1975a,b) that the antiobesity drug fenfluramine in therapeutic concentrations causes a significant and dose related increase in glucose uptake into isolated rat and human skeletal muscle in the presence of insulin.

Using the rat hemidiaphragm preparation and fenfluramine (100 ng/ml), we have investigated the effect of a series of receptor blocking drugs (atropine, haloperidol, mepyramine, methysergide, propranolol and thymoxamine) on this phenomenon. The results (Table 1) show that only the 5-HT antagonist, methysergide, blocked the action of fenfluramine and that this effect was dose related occurring with relatively low concentrations. 10 ng/ml caused approximately 40% inhibition, the maximal response from earlier work being $+2.4 \pm 0.60$ mg of glucose/g wet weight of tissue in 90 min (Kirby & Turner, 1975b).

The results are in agreement with earlier work, in which methysergide was shown to block fenfluramine-induced contractions of human isolated saphenous vein (Kirby & Turner, 1971) and also with the evidence that the central effects of fenfluramine are mediated via 5-HT mechanisms (Garattini, Bizzi, de Gaetano, Jori & Samanin, 1975).

Table 1 Effect of antagonist on fenfluramine-induced glucose uptake into the rat hemidiaphragm

		Change with antagonist when compared with:	
Antagonist	*Concentration (ng/ml)*	*(a) Insulin** *Response*	*(b) Insulin + fenfluramine** *Response*
Methysergide	250	-0.18 ± 0.46	-1.90 ± 0.19**
	50	—	-1.98 ± 0.45*
	10	—	-0.87 ± 0.13*
	2	—	0.15 ± 0.12
Atropine	250	-0.13 ± 0.46	-0.05 ± 0.21
Haloperidol	250	-0.77 ± 0.45	-0.17 ± 0.17
Mepyramine	250	$+0.12 \pm 0.28$	$+0.12 \pm 0.17$
Propranolol	250	-0.58 ± 0.46	-0.18 ± 0.34
Thymoxamine	250	-0.18 ± 0.24	$+0.30 \pm 0.50$

* Change expressed as mg of glucose taken up/g wet weight of tissue in 90 min ± s.e. mean, insulin concentration 100 μu/ml, fenfluramine concentration 100 ng/ml, $n=6$ for all groups.
*$P < 0.01$; **$P < 0.001$ using paired t-test.

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Some effects of D600, nifedipine and sodium nitroprusside on electrical and mechanical activity in rat portal vein

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In rat portal vein it has been proposed that contraction is associated with the release of superficially-bound Ca^{2+} and that this release is triggered by extracellular Ca^{2+} (Sigurdsson, Uvelius & Johansson, 1975). In the present experiments the effects of the so called calcium antagonist D600 [methoxyverapamil; 5-methyl-4-cyan-4-(3,4,5-trimethoxyphenyl)1-*N*-methyl-*N*-β-3,4-dimethoxy-phenylethyl)-aminohexane hydrochloride; Knoll], nifedipine [4-(2'-nitrophenyl)-2,-6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine; BAY a 1040, Bayer] and sodium nitroprusside on the electrical and mechanical activity of rat portal vein have been examined.

In normal physiological salt solution (PSS, containing 25 mM bicarbonate buffer, bubbled with 95%O_2/5%CO_2) both D600 (0.01–1 μM) and nifedipine (0.001–0.1 μM) shifted the noradrenaline dose-response curve to the right with a reduction in the maximum response. Sodium nitroprusside (0.1–10 μM) had no significant effect. Using a modified PSS (containing 10 mM MOPS [3-(*N*-morpholino) propanesulphonic acid; Calbiochem] buffer, bubbled with 100% O_2), the inhibitory effects of both D600 and nifedipine were antagonized by increasing the calcium concentration in the PSS (up to 80 mM).

The effects of the calcium antagonists on the mechanical and extracellularly-recorded electrical activity evoked by noradrenaline (1 μM; approximately an ED_{80}) were studied using a perfused capillary similar to that described by Golenhofen & v. Loh (1970). A Grass polygraph was used and the electrical and mechanical records were mathematically integrated to provide a quantitative measurement of drug responses. Sodium nitroprusside (0.1–10 μM) had no significant effect. D600 (0.01–1 μM) and nifedipine (0.001–0.1 μM) both reduced the mechanical activity evoked by noradrenaline (1 μM) to the same extent as observed in the tissue bath experiments. However, neither agent produced a reduction in electrical activity comparable with this reduction in mechanical activity. The degree of this electro-mechanical uncoupling was greater in the presence of nifedipine than in the presence of D600. When the electrical and mechanical responses produced by noradrenaline (1 μM) were examined in the presence of phentolamine (0.01–0.32 μM), both were similarly reduced. Higher concentrations of D600 (10 μM) and of nifedipine (1 μM) produced greater inhibition of spontaneous and noradrenaline-evoked electrical activity.

These results suggest that low-moderate concentrations of D600 and nifedipine prevent extracellular Ca^{2+} from triggering the release of Ca^{2+} from superficially-bound calcium stores. Higher concentrations, which reduce electrical activity to a greater extent are also able to antagonize transmembrane calcium flux. The inability of sodium nitroprusside to antagonize the phasic mechanical activity in rat portal vein is consistent with the work of Kreye, Baron, Lüth & Schmidt-Gayk (1975). These workers showed that sodium nitroprusside was most effective in antagonizing tonic mechanical responses in tissues where contraction was associated with a pool of calcium relatively independent of extracellular Ca^{2+}.

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