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CICLAZINDOL AND MAZINDOL ON GLUCOSE UPTAKE INTO HUMAN ISOLATED SKELETAL MUSCLE: NO INTERACTION OF MAZINDOL WITH METHYSERGIDE

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1 Ciclazindol, like mazindol, produced a significant concentration-dependent increase in glucose-uptake into human skeletal muscle in both the presence and absence of insulin.

2 Methysergide, which inhibits the action of fenfluramine on glucose-uptake into skeletal muscle, did not influence the effect of mazindol.

Introduction

Fenfluramine and its main metabolite norfenfluramine (Kirby, 1974; Kirby & Turner, 1974a), flutiorex (Kirby, Carageorgiou-Markomihelakis & Turner, 1975), S422 (Kirby, 1975) and mazindol (Kirby & Turner, 1976a) significantly increase glucose uptake into human isolated skeletal muscle, while amphetamine (Kirby & Turner, 1974b) has no significant effect. However, the mechanism of action for mazindol appears to be different from that of fenfluramine, norfenfluramine and flutiorex in that it does not require the presence of added insulin in the incubation medium for maximal activity. This has now been investigated further in two ways; firstly, ciclazindol (10-(*m*-chlorphenyl)-2,3,4,10-tetrahydro-pyrimido (1,2-a) indol-10-ol hydrochloride), a compound structurally related to mazindol (Figure 1) has been studied on this experimental preparation. Secondly, the effect of methysergide on the glucose uptake by mazindol has been studied as Kirby & Turner (1976b) have shown that the effect of fenfluramine is inhibited by this 5-hydroxytryptamine antagonist.

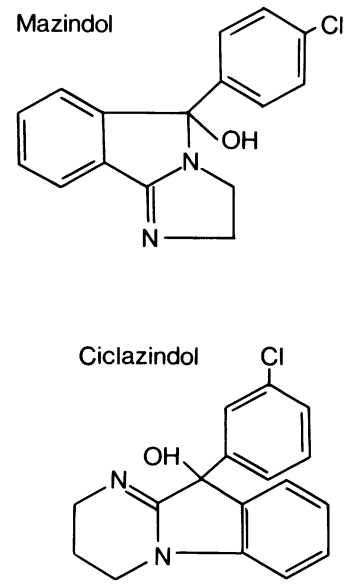

Figure 1 Structural formulae of mazindol and ciclazindol.

Method

The preparation of the muscle, incubation and estimation of glucose uptake were as described by Kirby, Leighton & Turner (1976). Human gluteus maximus or medius muscle was obtained at surgery for total hip replacement. Six or more parallel muscle strips of wet weight 80–132 mg were prepared from each muscle sample so that dose-response curves could be determined. The concentrations of ciclazindol were 0, 10, 50, 100, 500 and 1000 ng/ml. Incubation was carried out in Krebs bicarbonate buffer for 90 minutes. In the second series of experiments the effect of methysergide 5, 10, 50, 100 and 500 ng/ml was studied against mazindol in a concentration of 100 ng/ml which had been found in a previous study (Kirby & Turner, 1976a), to produce maximal increase in glucose uptake.

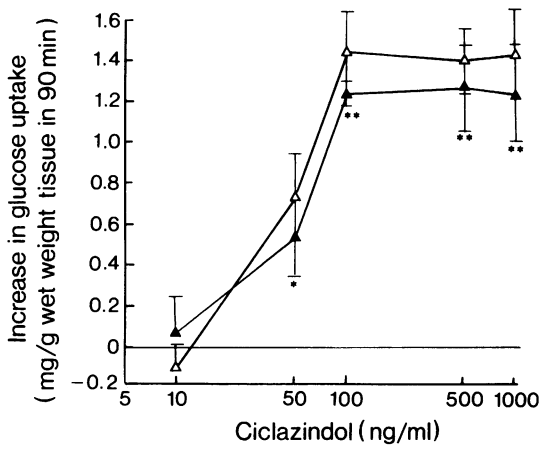

Figure 2 Dose-response curves (Mean ± s.e. mean, $n=5$) for ciclazindol on glucose uptake into human isolated skeletal muscles in the presence (▲) and absence (△) of insulin (100 μU/ml). * Indicates significant differences from control, $P<0.05$. ** Indicates significant differences from control, $P<0.01$.

Results

Dose-response curves obtained in the presence and absence of insulin (100 μU/ml) are shown in Figure 2, each point being the mean of five observations. It can be seen that ciclazindol caused a similar and significant increase in glucose uptake in both the presence and absence of insulin. The magnitude of the maximum response with ciclazindol is similar to that reported earlier with fenfluramine, norfenfluramine, flutiorex and mazindol. However, like mazindol this response was not dependent upon the presence of added insulin. Table 1 shows that methysergide did not influence the effect of mazindol on glucose uptake.

Table 1 Effect of methysergide on glucose uptake into human isolated skeletal muscle in the presence of mazindol and insulin

	*Change compared with methysergide compared with control**				
	Methysergide (ng/ml)				
Control value	*5*	*10*	*50*	*100*	*500*
6.1	−0.6	−0.5	−0.5	+0.1	+0.1
5.0	0.0	+0.4	+0.4	+0.3	+0.3
4.6	+0.2	+0.2	+0.3	−0.1	−0.3
4.9	−0.2	+0.1	−0.1	+0.2	−0.2

* Control glucose uptake (mg glucose/gram wet weight of muscle in 90 min) in the presence of mazindol (100 ng/ml) and insulin (100 μU/ml).

Discussion

These results show that ciclazindol, like the related compound mazindol, increases glucose uptake into skeletal muscle, and that this effect is not dependent on the addition of insulin to the incubation medium. The effect of mazindol is not influenced by the addition of methysergide in concentrations corresponding to, and in excess of, those probably reached in the plasma after therapeutic doses, namely 8.5–60 ng/ml (Meier & Shreier, 1976).

These appear, therefore, to be at least two basic mechanisms by which antiobesity drugs increase glucose uptake into human skeletal muscle. Table 2 shows that the group of fenfluramine, norfenfluramine, S422 and flutiorex all require the presence of added insulin to produce a maximum effect, and that the effect of fenfluramine is inhibited by methysergide in therapeutic concentrations (Kirby & Turner, 1976b). Ciclazindol and mazindol on the other hand, do not require the addition of insulin, and the action of mazindol is not reduced by methysergide.

It is tempting to relate these different profiles of activity to certain structural and pharmacological properties of these groups of drugs. Fenfluramine, norfenfluramine, S422 and flutiorex differ from amphetamine, which does not increase glucose uptake (Table 2), by possessing a trifluoromethyl substituent on the phenyl ring. Furthermore, there is considerable evidence that the central effects of fenfluramine are mediated through 5-HT mechanisms (Garattini, Bizzi, de Gaetano, Jori & Samanin, 1975), and Kirby & Turner (1971) found that fenfluramine-induced contractions of human isolated saphenous

Table 2 Classification of antiobesity drugs according to their effects on glucose uptake into skeletal muscle, and their interactions with methysergide

	Effect on glucose uptake with		
Drug	*No insulin*	*Insulin (100 μU/ml)*	*Methysergide*
Amphetamine	−	−	N.D.
Fenfluramine	−	+	I
Norfenfluramine	−	+	ND
Flutiorex	−	+	ND
S422	ND	+	ND
Mazindol	+	+	U
Ciclazindol	+	+	ND

ND, Not done; I, inhibited; U, unaltered; +, Increase in glucose uptake; −, no effect on glucose uptake.

vein were blocked by methysergide. Mazindol and ciclazindol are structurally unrelated to amphetamine or fenfluramine, and Kruk & Zarrindast (1976) have shown in the rat brain that mazindol was more potent than fenfluramine in affecting the uptake and release of dopamine while fenfluramine and norfenfluramine were more potent in affecting uptake and release of 5-HT. It would be of interest, therefore, to study the influence of a specific dopamine receptor blocking drug upon the facilitatory effect of mazindol or ciclazindol on glucose uptake into skeletal muscle.

The importance of these peripheral metabolic actions in the therapeutic activity of these drugs must await further elucidation.

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