THE ANORECTIC ACTION OF MAZINDOL

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Summary

MAZINDOL is an example of a non-phenylethylamine compound which nevertheless exhibits a biochemical and behavioural profile similar to that of d-amphetamine. Pharmacological analysis has implicated a possible role for dopaminergic mediation in the reduction of food-intake produced by mazindol. However, side-effects, including changes in general locomotor activity, are important factors to consider in relation to the anorectic activity of pharmacological agents. Mazindol reduces food-intake and this effect is antagonized by spiroperidol, a dopamine receptor blocker, even when both agonist and antagonist are given at doses which do not alter locomotor activity. Monitoring the anorectic action of drugs in a free-feeding situation, in relation to the distribution of eating and non-eating episodes, is suggested as a valuable method for understanding the basis of anorexia. Furthermore, concurrent monitoring of additional behavioural responses, including drinking behaviour and locomotor activity, should add considerably to a full account of the mechanisms of action by which drugs reduce food intake.

Introduction

The use of pharmacological agents in the clinical control of obesity is, at present, common practice. Resort to the use of drugs which suppress appetite (anorectic drugs) has been the result of the common failure of daily nutrient-intake reduction purely by dietary restrictions, a theoretically adequate approach, to control weight reduction in non-pathologically obese subjects (Maikel and Zabik, 1977). Amphetamine is the prototype of a class of a-methyl-phenylethylamine drugs which has provided the majority of clinical anorexigenic agents over the past 40 years. Unfortunately, the undesirable central nervous system stimulant properties of many of these drugs, illustrated by the notoriety of amphetamine as a drug of abuse, has limited their clinical potential.

A recent review by Hoebel (1977) illustrates how in the development of new anorectic drugs, modifications of the basic phenylethylamine structure have provided drugs with varying excitatory and anorectic potency. While many of these drugs have actions in the periphery or effects on the metabolism of energy substrates, focus on the brain mechanisms involved in their action has yielded much valuable information not only with regard to the basis of their anorectic action but also on the central pathways involved in the control of feeding behaviour.

Mazindol (MZL) is a new drug which is clinically potent as an anorectic agent (Wallace and Chir, 1976; Allen, 1977). It differs from most in that it is not a phenylethylamine derivative, and it has been described as having weak central nervous system stimulant properties with marked anorectic potency (Gogerty et al., 1975). There is much similarity in the biochemical and behavioural actions of mazindol and amphetamine-like compounds and considerable evidence points to a role for monoamine neurotransmitter systems particularly the catecholamines, in the anorectic effect of both.
Biochemical Effects of Mazindol

Gogerty et al (1975) suggested that ability of mazindol to inhibit the re-uptake of norepinephrine (NA) is the basis of its mechanism of action. However Koe (1976) has shown that mazindol is, in addition, a potent uptake inhibitor of dopamine (DA) and serotonin (5HT), in synaptosomal preparations. Mazindol is also a weak releasing agent for labelled DA and 5HT from synaptosomal preparations (Carruba et al, 1977a; Kruk and Zarrindast, 1976b), and is more potent both as an uptake inhibitor and releaser of DA than 5HT (Kruk and Zarrindast, 1976b). Kruk and Zarrindast (1976b) suggest that NA mechanisms are unlikely to have a significant role in mediating the anorectic responses of this drug. Mazindol may owe at least part of both its stimulant and anorexic properties to its capacity to block uptake of synaptically released DA (Heikkila et al, 1977).

In the studies of the in vivo turnover rate of catecholamines Carruba et al (1976) found that, in behaviourally active doses, mazindol increased DA turnover in the caudate nucleus. 5HT turnover was unaffected while that of NA was decreased by the drug. Therefore it is possible that increased synthesis and release of DA from nerve terminals may also be an important mechanism of mazindol action.

Depletion of brain 5HT by p-chloromethamphetamine (Carruba et al, 1977b) or fenfluramine (Samanin et al, 1977) is also inhibited by mazindol suggesting that 5HT neuronal systems may also play a part in the drug action.

Behavioural Effects of Mazindol

Mazindol exhibits a behavioural profile similar to that of d-amphetamine. In rats it produces anorexia, increases motor activity and body temperature, produces stereotyped behaviour at high doses and induces ipsilateral turning in unilaterally striatal-lesioned animals (Zambotti et al, 1976). A common approach in determining the role played by various neurochemical systems in the action of anorectic agents has been to examine anorectic potency following destruction, transmitter depletion or synthesis inhibition, or receptor antagonism in specific monoamine systems. It has been suggested that d-amphetamine anorexia may be mediated by activation of DA neural systems while fenfluramine anorexia may depend specifically on 5HT mechanisms (Kruk, 1973). This contention is supported by the finding that preferential destruction of DA systems antagonises d-amphetamine anorexia, while selective 5HT destruction does not, but enhances the anorectic potency of fenfluramine (Hollister et al, 1975). The existence of a clear distinction between the neural mechanisms underlying amphetamine and fenfluramine anorectic action is widely supported (Garattini et al, 1975). In this respect mazindol resembles amphetamine in requiring the presence of catecholamines as chemical mediators of its anorectic action (Garattini et al, 1975).

The anorexia induced by mazindol has been completely antagonised with the dopamine blocker pimozide and partially antagonised by synthesis inhibition using $\alpha$-methyl-p-tyrosine (Zambetti et al, 1976). Furthermore it was not possible to antagonise mazindol anorexia with pretreatment with either an $\alpha$- or $\beta$-adrenoreceptor blocker or a 5HT receptor blocker (Kruk and Zarrindast, 1976a). An intrastriatal injection of the neurotoxin 60HDA which produced a selective reduction of striatal DA markedly reduced the anorectic effect of mazindol (Samanin et al, 1977). These results are consistent with the hypothesis that brain DA may contribute significantly to the anorectic action of mazindol. Although some authors have suggested that 5HT mechanisms in the brain may normally serve to inhibit feeding (Breish et al, 1976; Blundell, 1977), the absence of any