Some effects of mazindol on the metabolism of monoamines in the rat brain

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Animal and human studies have shown mazindol (5-hydroxy-5-(4'-chlorophenyl)-2,3-dihydro-5H-imidazo-(2,1-a)isoindole) to be an effective anorectic agent (Goldrick, Nestel & Havenstein, 1974; Gogerty, Penberthy, Iorio & Trapold, 1975; Haugen, 1975). Brain monoamines have been implicated in the mechanism of action of anorectic drugs. For example, it has been proposed that 5-hydroxytryptamine and catecholamines play an important role in the anorectic effect of fenfluramine and (+)-amphetamine respectively (Garattini, Bizzi, de Gaetano, Jori & Samanin, 1975). The objective of this study was to investigate some of the effects of mazindol on the metabolism of 5-hydroxytryptamine, noradrenaline and dopamine in the rat brain.

Male Wistar rats weighing 180–220 g were used in all studies. Mazindol (30 mg/kg, i.p.) had no effect on steady state levels of 5-hydroxytryptamine, 5-hydroxyindole acetic acid or tryptophan in the rat brain at 1,2 and 4 h after injection. The turnover of 5-hydroxytryptamine in the brain was also unaltered by mazindol. The *in vivo* blockade of rat brain 5-hydroxytryptamine re-uptake was studied by investigating the effect of drug pretreatment on the ability of *p*-chloroamphetamine (10 mg/kg, i.p.) to lower brain 5-hydroxytrytamine content. Unlike compounds which block 5-hydroxytryptamine re-uptake, e.g. the tricyclic antidepressants, mazindol (30 mg/kg, i.p.) did not antagonize the *p*-chloroamphetamine induced reduction in the concentration of brain 5-hydroxytryptamine.

Mazindol (30 mg/kg, i.p.) evoked a slight but significant decrease in rat brain steady state levels of both noradrenaline and dopamine. *In vivo* central catecholamine re-uptake was studied by investigating the effect of drug pretreatment on the ability of intraventricularly administered 6-hydroxydopamine to lower brain levels of noradrenaline and dopamine. Both mazindol and desipramine antagonized the ability of intraventricularly administered 6-hydroxydopamine (100 μg) to lower brain steady state levels of noradrenaline. Mazindol was approximately five times more potent than desipramine. The ability of intraventricularly administered 6-hydroxydopamine (250 μg) to lower rat brain dopamine content was unaltered by the prior administration of desipramine (30 mg/kg, i.p.). In contrast to desipramine, mazindol was a potent inhibitor of the 6-hydroxydopamine induced fall in brain dopamine concentration, the i.p. ID_{50} value for mazindol being 10.3 mg/kg. In addition to blocking dopamine re-uptake, mazindol like (+)-amphetamine (Dorris & Shore, 1974), also released dopamine as indicated by its ability to lower levels of α-methyl-*m*-tyramine in the rat corpus striatum.

The results of this study reveal that mazindol is a potent inhibitor of the *in vivo* re-uptake of both noradrenaline and dopamine in the rat brain. In addition to blocking dopamine re-uptake, mazindol also releases the amine. In contrast to its marked effects on brain catecholaminergic systems, mazindol would appear to be devoid of effect on rat brain serotoninergic systems. The neurochemical profile of mazindol bears a much closer resemblance to that of (+)-amphetamine than to that of fenfluramine.

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