On the interaction between pimozide and α-methyltyrosine

Neuroleptic drugs of the phenothiazine and butyrophenone groups are widely used in the treatment of various psychiatric disorders. We have found that the behavioural effect, i.e. depression of food-reinforced lever-pressing, of the butyrophenone derivative haloperidol in rats was markedly potentiated by pretreatment with the tyrosine hydroxylase inhibitor α-methyl-*p*-tyrosine (α-MT) (Ahlenius & Engel, 1971), and these results suggested an alternative possibility for treating certain mental disorders. Recently Carlsson, Persson & others (1972) reported that the antipsychotic action of chlorpromazine and thioridazine was markedly potentiated when combined with α-MT, permitting a marked reduction of the neuroleptic dosage required for controlling the condition in patients suffering from chronic schizophrenia. Considerable evidence indicates that phenothiazines and butyrophenones accelerate the turnover of the catecholamines, probably via a feedback mechanism as a consequence of the blocking action of these drugs on central catecholamine receptors (see Andén, Carlsson & Häggendal, 1969). One explanation of the potentiation obtained could be an inhibition by the tyrosine hydroxylase inhibitor of the neuroleptic induced increase in catecholamine turnover. However, the possibility that the two agents may interfere with each other's metabolism could not be excluded in these investigations. The present experiments were undertaken to investigate this.

Three male Sprague-Dawley rats, 280–290 g, were kept at 80% of their free feeding weight and trained to press a lever to obtain food in standard behavioural chambers (Grason-Stadler, Mass., USA). The animals after initial training, were maintained on a fixed ratio 40 schedule (FR 40), *i.e.* every 40th lever press will produce a food-pellet (Noyes, 45 mg). This schedule generates a high and stable rate of responding (Ferster & Skinner, 1957). Responses and reinforcements were recorded on digital counters and cumulative recorders. The rats were exposed to daily sessions of 30 min 5 days a week. Drug administration was not begun until a stable behavioural baseline was established for each animal. Drugs were injected on Tuesdays and Fridays, the remaining days, including the day before the first injection and the day after the last, served as control sessions.

Pimozide (Janssen, Beerse), a neuroleptic of the diphenylbutylpiperidine-group, was given intraperitoneally 6 h before the behavioural test. The drug was dissolved in a few drops of acetic acid and the final solution made up with 5·5% glucose. The methylester hydrochloride of α-methyl-*p*-tyrosine (α-MT, H 44/68, Hässle, Mölndal) was given intraperitoneally 4 h before the behavioural tests. The doses are given in Table 1.

From pilot experiments, the highest ineffective doses of pimozide and α-MT were found to be 0·08 mg kg^{-1} (i.p.) and 40 mg kg^{-1} (i.p.), respectively.

The intraperitoneal injection of pimozide (0·08 mg kg^{-1}) had no effect on the lever-pressing behaviour in the rats tested 6 h after the injection. Likewise, α-MT (40 mg kg^{-1}) was ineffective 4 h after the injection. The combined treatment of pimozide and α-MT in doses that were reduced to half, i.e. 0·04 and 20 mg kg^{-1}, respectively, resulted in a statistically significant decrease in the lever-pressing rate of the three rats (Table 1; Fig. 1).

The neuroleptic drug haloperidol used in our earlier experiment (*vide supra*) has a half-life of 3 h. In the present experiment we have used pimozide, a neuroleptic drug with a different chemical structure and with a longer half-life (10 h) (Janssen, Niemegeers & others, 1968). Since pimozide in combination with α-MT resulted in the same degree of potentiation as haloperidol plus α-MT (see Ahlenius & Engel, 1971), it seems less likely that α-MT interferes with the metabolism of these two drugs.

The possibility that pimozide increased the brain concentrations of α-MT was

Table 1. *Performance of rats on a food reinforced fixed ratio 40 : 1 schedule after pimozide* (0·08 mg kg^{-1}) *or* α-*MT* (40 mg kg^{-1}) *or pimozide* + α-*MT* (0·04 + 20 mg kg^{-1}); *and tyrosine content* (μg g^{-1} mean ± s. d.) *in rat brain after saline and pimozide* (0·08 mg kg^{-1}) *and the tyrosine* + α-*MT content after* α-*MT* (80 mg kg^{-1}) *alone or together with pimozide* (80 + 0·08 mg kg^{-1}).

Parameter	Control/saline	Pimozide	α-MT	Pimozide + α-MT
	A	B	C	D
Lever presses per second (mean of 3 rats) ..	2·5	2·2	2·5	1·3
Tyrosine content ..	12·71 ± 1·16 (n = 4)	11·39 ± 0·57 (n = 4)	—	—
Tyrosine + α-MT content ..	—	—	21·40 ± 1·46 (n = 4)	21·07 ± 0·65 (n = 4)

t-test after analysis of variance (Winer, 1962):
Lever pressing: A—B, A—C, B—C, N.S. ($P>0·05$); A—D, B—D, C—D ($P<0·05$).
Tyrosine, and tyrosine + α-MT: A—B, C—D, N.S. ($P>0·05$); A—C, A—D, B—C, B—D ($P<0·001$).

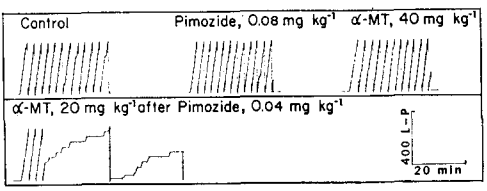

FIG. 1. Cumulative records of one animal showing the rates of lever pressing. The short downward deflections on the records indicate the delivery of food. L-P = lever pressers.

investigated by measuring the brain levels of α-methyltyrosine after pretreatment with pimozide. A separate group of 16 male Sprague-Dawley rats, 250–300 g, was used. Pimozide was injected 6 h, and/or α-MT 4 h, before decapitation. The whole rat brain, with the exception of the olfactory bulbs, was rapidly removed. Tyrosine and α-MT was analysed spectrofluorimetrically (Waalkes & Udenfriend, 1957) after homogenization and extraction of the tissue in ice-cold 0·4% perchloric acid and cation-exchange chromatography (Kehr, Carlsson & Lindqvist, 1972). The α-MT was calculated as the difference between the combined tyrosine plus α-MT concentrations in α-MT-treated rats and the tyrosine concentrations in the control animals (see Table 1). α-MT was found to give an identical fluorescence intensity to that of an equivalent amount of tyrosine in the tyrosine assay. The accumulation of α-MT in brain after pretreatment with pimozide did not differ from that obtained after α-MT alone (Table 1), indicating that pimozide does not interfere with the metabolism of α-MT. Interestingly the dose of α-MT used, 80 mg kg^{-1}, was the lowest dose found to result in increased tyrosine readings.

In conclusion, the present results do not support an interpretation in terms of an interference at the metabolic level as a cause of the potentiation of the behavioural effects in man and animals observed after the combination of neuroleptic drugs and α-MT (Ahlenius & Engel, 1971; Carlsson & others, 1972).

Furthermore, these experiments point to the importance of an undisturbed dopamine neurotransmission for conditioned behaviour, since pimozide has been shown to be a relatively selective blocking agent of the central dopamine receptor (Andén, Butcher & others, 1969).

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Blocking effect of α-methyltyrosine on amphetamine based reinforcement

The intravenous injection of amphetamine-like drugs into man causes characteristic euphoric sensations which are commonly regarded as the basis for drug dependence of the amphetamine type (Eddy, Halbach, & others, 1965). Recent clinical studies (Jönsson, Gunne & Anggard, 1969; Jönsson, Anggard & Gunne, 1971) have shown this subjective euphoric action of (±)-amphetamine to be blocked by α-methyltyrosine, an inhibitor of tyrosine hydroxylase which had previously been found to block the behavioural effects of amphetamine in laboratory species (Weissman & Koe, 1965; Hanson, 1966; Randrup & Munkvad, 1966). Although the euphoric effect of amphetamine-like drugs has been equated with their experimental effect of serving as primary positive reinforcers (Wikler, 1971; Renault & Schuster, 1972; Crowley, 1972), it has not been shown experimentally that α-methyltyrosine (α-MT) can block the reinforcing action of such drugs. Modification of the self-administration behaviour of rats for methamphetamine by α-MT treatment has been reported by Pickens, Meisch & Dougherty (1968). While the authors tentatively suggested that behaviour alterations seen were attributable to a reduction by α-MT of the effectiveness of methamphetamine as a reinforcer, no firm conclusion could be drawn from their preliminary investigation concerning the basis for the observed effects.

There are a number of problems in studying an influence of one drug on the reinforcing effect of another by techniques which measure effects simply in terms of increases or decreases from ongoing operant self-administration baselines. To obviate ambiguities that arise in the interpretation of such results, the present experiments utilized a two-phase design new to self-administration studies (Davis & Smith, 1972). In the first phase, effects of a test agent on primary reinforcement are assessed