Reversal by a central antiacetylcholine drug of pimozide-induced inhibition of mouse-jumping in amphetamine-dopa treated mice

We recently reported (Lal, Colpaert & Laduron, 1975) that a combination of amphetamine and L-3-4-dihydroxyphenylalanine (L-dopa) reliably elicits mouse-jumping. The jumping thus produced is unaffected by phentolamine, is enhanced by aminophylline (Colpaert & Lal, 1974) and is blocked by haloperidol and pimozide in a dose-dependent manner (Lal & others, 1975). We now report that this blocking action of neuroleptics is reversed by dexetimide, a centrally acting anti-acetylcholine drug (Janssen & Niemegeers, 1967).

Male, albino mice, random bred of the Swiss Webster strain, 23–25 g, and fasted overnight, were used. (±)-Amphetamine sulphate and dexetimide were dissolved in distilled water, L-dopa was suspended in 2% carboxymethyl cellulose and pimozide was dissolved in 0·3% tartaric acid. All solutions were freshly prepared immediately before injection. L-Dopa and amphetamine were injected intraperitoneally while pimozide and dexetimide were given subcutaneously.

Mouse jumping was determined by counting each jump after the mice were placed singly in glass jars (21 cm high, 14 cm diameter), covered with clear plastic which prevented escape but left spaces for air circulation. Simultaneous lifting of all four paws in one action was taken as a jump response. Since up to 4 jumps were seen in less than 5% saline treated mice, more than 4 jumps after amphetamine plus L-dopa administration were used as a criterion for a positive jump-response.

As reported by Lal & others (1975), the combined administration of amphetamine and L-dopa elicited intense jumping in the mice and pimozide blocked this jumping (Table 1). Dexetimide itself neither produced any jumping in naive mice nor did it affect the jumping induced by amphetamine and L-dopa. However, pretreatment with dexetimide clearly produced a reversal of the pimozide-induced inhibition of jumping even when pimozide was administered in doses which were previously shown (Lal

Table 1. *The differential effects of dexetimide and isopropamide on inhibition of jumping caused by pimozide in mice treated with amphetamine and* L-*dopa.*[1]

Group	Drug	Dose (mg kg^{-1})	N	Jumping counts 30 min[2] % positive	Median jumps	Average deviation[3]	P[4]
I	Saline[1]	—	8	89	358	77	—
II	Dexetimide[5]	2·5	4	100	314	202	>0·05(*vs* I)
III	Pimozide[6]	2·5	9	7	0	2	<0·001(*vs* I)
IV	Pimozide	0·63	15	22	0	35	<0·001 (*vs* I)
V	Pimozide+ dexetimide	2·5 2·5	9	67	253	48	<0·05 (*vs* III)
VI	Pimozide+ dexetimide	0·63 2·5	9	67	302	81	<0·001 (*vs* IV)
VII	Pimozide+ isopropamide	2·5 5·0	9	0	0	0	>0·05 (*vs* III)

[1]All mice were injected with amphetamine (4 mg kg^{-1}) 15 min before and L-dopa (400 mg kg^{-1}) immediately before measurement.
[2]Jumping responses were counted for 30 min. 15 min after amphetamine and immediately after L-dopa injection.
[3]Highest number of jumps—lowest number of jumps, divided by number of mice tested.
[4]Statistical comparisons are done by means of the Mann-Whitney U-test, two tailed.
[5]Injected 45 min before amphetamine and 60 min before L-dopa.
[6]Injected 165 min before amphetamine and 180 min before L-dopa.

& others, 1975) to be 4–8 times higher than its effective blocking dose. Isopropamide, a peripherally acting anti-acetylcholine drug (Janssen & Niemeggers, 1967) did not resemble dexetimide in reversing pimozide action, suggesting that the dexetimide action was centrally mediated.

A relation between central dopaminergic and cholinergic systems has been previously suggested by many studies. For instance, a number of distinct actions of neuroleptics can be reversed by appropriate doses of antiacetylcholine drugs. This antagonism is seen in catalepsy (Morpurgo & Theobald, 1964), inhibition of avoidance responding (Hanson, Stone & Witoslawski, 1970), inhibition of brain self stimulation (Wauquier, Niemegeers & Lal, 1975), increase of striatal dopamine turnover (Bowers & Roth, 1972; Puri, Reddy & Lal, 1973), and certain clinical side effects as well as therapeutic actions (Haase & Janssen, 1965; Singh & Smith, 1973) produced by neuroleptic drugs. These observations suggest that the described actions of neuroleptic drugs involve an interaction with a cholinergic system which is inhibited by dopamine stimulation of critical brain areas. The present data with jumping behaviour support the above hypothesis and are consistent with the assumption that jumping behaviour may involve inhibition of certain cholinergic systems through the stimulation of dopamine receptors. However, it is not yet clear why antiacetylcholine drugs themselves do not cause jumping in naive animals. Perhaps the jumping response is mediated by a cholinergic system which is selectively controlled by dopaminergic activity.

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