Different sensitivity to drugs eliciting homovanillic acid increase in two strains of mice

It was previously reported that mice of the C3H strain have relatively little sensitivity to the pharmacological and biochemical effects produced by (+)-amphetamine (Dolfini, Garattini & Valzelli, 1969; Dolfini, Ramirez del Angel & others, 1970; Jori & Garattini, 1973). Of interest was the observation that amphetamine showed little activity in eliciting an increase of homovanillic acid (HVA) in the striatum of C3H mice in respect to a standard strain (Swiss mice) (Caccia, Cecchetti & others, 1973) although the concentrations of amphetamine in the striatum are comparable (Jori & Caccia, unpublished observations). The amphetamine-induced increase of the HVA is considered the consequence of an increased dopamine release at the presynaptic level. Indeed, in the striatum, amphetamine releases dopamine (Carlsson, 1970), it blocks the dopamine uptake (Fuxe & Ungerstedt, 1970) and it increases dopamine turnover (Costa & Groppetti, 1970; Javoy, Hamon & Glowinsky, 1970). In order to better understand the insensitivity to the elevation of HVA elicited by amphetamine in C3H mice, we have now studied the effect of various drugs which can bring about an increase in the concentration of this dopamine metabolite, using this same animal strain. Female mice of C3H and CD1 strains were given intraperitoneally several drugs at various doses. The drugs were: (+)-amphetamine and *N*-methylamphetamine, kindly supplied by Recordati, Milan, (−)-fenfluramine (Laboratories Servier, Orléans), chlorpromazine (Farmaceutici Italia, Milan), haloperidol (Janssen Pharmaceutica, Beerse); methadone (Burroughs Wellcome, London), diethylpropion (Richardson Merrel, Naples), mazindol (Sandoz Pharmaceuticals, Hanover).

Animals were killed 1 h after treatment; brains were removed and the striatal areas dissected, frozen and stored at −20°. HVA was determined on three pooled striata by the method of Korf, Ottema & Van der Veen (1971).

The results in Table 1 indicate that C3H as well as CD1 mice were equally sensitive in showing an increase of striatum HVA after administration of most of the drugs used.

Table 1. *Effect of various drugs on the HVA concentrations of the striatum of CD1 and C3H mice.* Animals were killed 1 h after the administration of the drug. Each figure is the average of at least four determinations each one performed on a pool of three striata.

Treatment	mg kg^{-1} i.p.	Striatum HVA (ng g^{-1} ± s.e.) CD1 mice	C3H mice
Saline	—	248 ± 12	252 ± 9
(+)-Amphetamine sulph.	7·5	432 ± 20	295 ± 0·5*
	15	729 ± 19	526 ± 43*
N-Methylamphetamine HCl	7·5	495 ± 37	226 ± 28*
	15	403 ± 32	430 ± 14
(−)-Fenfluramine HCl	7·5	669 ± 67	739 ± 31
	15	—	751 ± 74
Chlorpromazine HCl	2·5	554 ± 64	493 ± 48
	5	—	1516 ± 178
Haloperidol	0·25	450 ± 72	453 ± 47
	1	911 ± 105	1016 ± 172
Methadone HCl	5	359 ± 64	622 ± 51**
Diethylpropion HCl	15	348 ± 14	335 ± 53
Mazindol	15	409 ± 41	461 ± 97

* = $P < 0.01$ versus CD1 mice; ** = $P < 0.05$ versus CD1 mice.

Chlorpromazine, fenfluramine, haloperidol, diethylpropion, and mazindol enhanced the striatum HVA to a similar extent in C3H and CD1 mice. The effect of methadone seems to be more evident in the C3H than the CD1 strain. It is also confirmed that amphetamine and methylamphetamine are inactive at 7·5 mg kg^{-1} in C3H mice. However, amphetamine is also significantly less active in this strain than in CD1 at 15 mg kg^{-1}.

The drugs tested have different mechanisms of action in elevating striatum HVA. It is believed that neuroleptic drugs such as chlorpromazine and haloperidol (Laverty & Sharman, 1965; Da Prada & Pletscher, 1966) and analgesics such as methadone (Sasame, Perez-Cruet & others, 1972; Gessa, Vargiu & others, 1973) increase the HVA concentrations because of an increase of dopamine turnover which is the consequence of inhibition of the dopamine receptors exerted by these drugs. We have previously reported that anorectic drugs such as amphetamine, fenfluramine, norfenfluramine, mazindol and diethylpropion are able to elevate the HVA concentrations in the striatum of rats (Jori & Bernardi, 1969; Jori & Dolfini, 1974). However, we have demonstrated that the mechanism of action of fenfluramine on dopamine metabolism is different from the one postulated for amphetamine yet is similar in action to the dopamine antagonists (Jori & Bernardi, 1972; Jori, Cecchetti & others, 1974).

The results reported here indicate that C3H mice can react with an increase of the striatum HVA to many drugs affecting the dopamine metabolism, but are specifically insensitive to the mechanism by which amphetamine and methylamphetamine interact with the dopaminergic neurons to induce HVA accumulation.

It remains to be established whether other anorectic drugs (mazindol, diethylpropion) increase striatum HVA with a mechanism of action similar to the one exerted by amphetamine or by fenfluramine.

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