Differential effects of the isomers of fenfluramine and norfenfluramine on rat striatal acetylcholine content

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Fenfluramine is a racemic compound made up of the optical isomers, (+)-fenfluramine and (—)-fenfluramine. When the racemate is administered in vivo each of the optical forms is metabolized in most animal species to its respective isomer of norfenfluramine (Garattini et al 1979). It has been shown that the (+)-forms of both fenfluramine and norfenfluramine were more active than the (—)-forms in their anorectic property, while both enantiomers of norfenfluramine were more active than the fenfluramine enantiomers (Garattini et al 1979).

Neuropharmacological effects of the four compounds are also different. The (—)-isomers are more effective than the (+)-forms in increasing striatal homovanillic acid (Jori et al 1973), which may denote dopamine receptor blockade. On the other hand, (+)-fenfluramine is the most active of the compounds in vitro in inhibiting uptake of 5-hydroxytryptamine (5-HT) and is as potent as (+)-norfenfluramine in releasing 5-HT from rat brain synaptosomes (Garattini et al 1979).

Another neuropharmacological property of (+)-fenfluramine is its capacity to increase the concentration of acetylcholine (ACh) in the striatum by a selective action on presynaptic 5-hydroxytryptaminergic nerve terminals (Ladinsky et al 1978; Samanin et al 1978). In relation to these findings it was of interest to compare the potency of the optical isomers of fenfluramine and norfenfluramine on striatal ACh.

All experiments were on female CD-COBS rats, 175–200 g (Charles River, Italy). The animals were decapitated and the head immediately immersed in liquid N_2 for 6–7 s. The striatum was dissected out under n-pentane at minus 5 °C, then frozen in liquid N_2, weighed and pulverized. ACh was determined by the radiochemical method of Saelens et al (1970) with some modifications (Ladinsky et al 1976).

As shown in Table 1, (+)-norfenfluramine is the most active compound in increasing striatal ACh, followed by (+)-fenfluramine and (—)-norfenfluramine while (—)-fenfluramine was inactive. It has been established (Duhault et al 1975); Garattini et al 1979 that (+)-fenfluramine is active mostly itself and not through an accumulation of (+)-norfenfluramine, at least at the 30 min time used in this experiment.

It is conceivable that also (+)-norfenfluramine's action on striatal ACh is mediated through the 5-hydroxytryptaminergic system because of its considerable effect on brain 5-HT mechanisms. (—)-Fenfluramine and (—)-norfenfluramine may not be active on striatal ACh because of their dual roles as releasers of 5-HT and blockers of dopamine receptors. Since dopamine receptor blockade leads to a decrease in striatal ACh (Consolo et al 1975) it may be held that (—)-fenfluramine's inactivity is the result of the two opposing effects.

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Table 1. Effect of the optical isomers of fenfluramine and norfenfluramine on rat striatal ACh.

Dose (mg kg^{-1}, i.p.)	Striatal ACh (nmol g^{-1} wet wt)			
	(+)-fenfluramine	(−)-fenfluramine	(+)-norfenfluramine	(−)-norfenfluramine
Saline	33·1 ± 0·9	32·8 ± 0·9	33·8 ± 1·0	33·9 ± 1·6
0·6	—	—	38·6 ± 1·4	—
1·25	35·1 ± 1·2	—	45·7 ± 2·1**	—
2·5	40·3 ± 1·7**	—	45·5 ± 2·6**	—
5	47·2 ± 1·8**	30·0 ± 1·5	43·2 ± 2·1**	37·2 ± 1·7
7·5	47·1 ± 1·5**	—	—	—
10	49·1 ± 3·4**	36·1 ± 1·4	41·0 ± 2·6*	38·8 ± 1·1*
15	—	30·6 ± 1·0	—	31·7 ± 1·3

** $P < 0.01$ vs respective saline group (Duncan's test).
* $P < 0.05$.
Assays were made 30 min after drug administration.
Data are mean ± s.e. of 8–12 rats.

REFERENCES

Consolo, S., Ladinsky, H., Bianchi, S. (1975) Eur. J. Pharmacol. 33: 345–351

Duhault, J., Malen, Ch., Boulanger, M., Voisin, C., Beregi, L., Schmitt, H. (1975) Arzneim.-Forsch. 25: 1755–1758

Garattini, S., Caccia, S., Mennini, T., Samanin, R., Consolo, S., Ladinsky, H. (1979) Curr. Med. Res. Opinion 6: Suppl. 1, 15–27

Jori, A., Dolfini, E., Tognoni, G., Garattini, S. (1973) J. Pharm. Pharmacol. 25: 315–318

Ladinsky, H., Consolo, S., Bianchi, S., Jori, A. (1976) Brain Res. 108: 351–361

Ladinsky, H., Consolo, S., Peri, G., Crunelli, V., Samanin, R. (1978) in: Jenden, D. J. (ed.) Cholinergic Mechanisms and Psychopharmacology, Plenum Press: New York, pp 615–627

Saelens, J. K., Allen, M. P., Simke, J. P. (1970) Arch. Int. Pharmacodyn. Ther. 186: 279–286

Samanin, R., Quattrone, A., Peri, G., Ladinsky, H., Consolo, S. (1978) Brain Res. 151: 73–82