(Fig. 1). The lack of any alteration in the NA/DA ratio due to DA concentration and the increase in the A/NA ratio corresponding to an increase in dopamine level suggest that in the adrenal gland this is an indicator of adrenaline synthesis. Racz et al (1984) have also demonstrated a similar relation between dopamine and adrenaline in the bovine adrenal gland.

Although the drugs were injected daily for ten days, the catecholamines were measured 24 h after the last injection. In this situation our observation may represent a 'rebound' phenomenon for bromocriptine, which has a shorter half-life then haloperidol.

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Effect of fluoxetine pretreatment on the neurochemical changes induced by amfonelic acid combined with spiperone in rats

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Combined treatment with amfonelic acid plus spiperone caused large increases in 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) and a decrease in dopamine in rat striatum. 5-Hydroxytryptamine (5-HT) was decreased in striatum (but not in hypothalamus), and 5-hydroxyindoleacetic acid (5-HIAA) was increased in the striatum. Pretreatment with fluoxetine, an inhibitor of uptake into 5-HT neurons, antagonized the decrease in 5-HT and the increase in 5-HIAA and in the ratio 5-HIAA/5-HT but did not antagonize the changes in dopamine or its metabolites. The amfonelic acid–spiperone combination apparently causes increased release of dopamine in striatum, and the released dopamine is accumulated by 5-HT nerve terminals via the membrane uptake carrier. Inhibition of that carrier by fluoxetine prevents the release of 5-HT caused by the dopamine influx.

Amfonelic acid, a non-amphetamine stimulant drug, causes a large increase in dopamine turnover in rat striatum when given in combination with classical neuroleptic drugs (Shore 1976). Waldmeier (1985) recently reported that the massive release of dopamine that occurred when amfonelic acid and a neuroleptic drug were given in combination, resulted in the accumulation of dopamine by 5-HT-containing nerve terminals in rat striatum, leading to depletion of 5-HT. That depletion was antagonized by citalopram, an inhibitor of 5-HT uptake. Our experiments, undertaken to confirm and extend those observations, revealed (1) that the decrease in 5-HT was accompanied by an increase in 5-HIAA in the striata of rats given amfonelic acid plus spiperone and (2) that the increase in the ratio 5-HIAA/5-HT was antagonized by fluoxetine, a selective inhibitor of 5-HT uptake, which did not antagonize the changes in dopamine metabolism.

* Correspondence.

Method

Male Wistar rats (HSD/[WI]BR), about 150 g, obtained from Harlan Sprague-Dawley, Inc., Cumberland, Indiana, received injections of spiperone (0·5 mg kg^{-1} i.p.) 90 min before they were killed and 5 min after

Table 1. Effect of amfonelic acid and spiperone on dopamine and 5-HT concentrations in rat striatum and hypothalamus.

	Monoamines, nmol g^{-1}			
	Striatum		Hypothalamus	
Treatment group	Dopamine	5-HT	Dopamine	5-HT
Control	80·7 ± 3·6	3 15 ± 0·14	1·46 ± 0·09	4·70 ± 0·18
Amfonelic acid + spiperone	47·4 ± 3·8 (−41%)*	1·57 ± 0·19 (−50%)*	1·40 ± 0·10 (n.s.)	4·36 ± 0·16 (n.s.)

* Significant difference from control group ($P < 0·05$).

those of Waldmeier (1985) who reported depletion of 5-HT and dopamine in striatum but no depletion of 5-HT in cortex. Table 2 shows that the decrease in 5-HT concentration in the striatum was accompanied by an increase in 5-HIAA concentration; the ratio 5-HIAA/5-HT was more than doubled in rats treated with amfonelic acid and spiperone. Fluoxetine pretreatment antagonized the changes in 5-HT and in 5-HIAA, resulting in the ratio 5-HIAA/5-HT being significantly lower than in rats treated only with amfonelic acid and

Table 2. Effect of fluoxetine pretreatment on amfonelic acid/spiperone-induced changes in 5-hydroxyindole concentrations in rat striatum.

	5-Hydroxyindoles in striatum, nmol g^{-1}		Ratio,
Treatment group	5-HT	5-HIAA	5-HIAA/5-HT
Control	3·15 ± 0·14	2·26 ± 0·09	0·72 ± 0·03
Amfonelic acid + spiperone	1·57 ± 0·19*	2·92 ± 0·13*	1·96 ± 0·24*
Amfonelic acid + spiperone + fluoxetine	2·10 ± 0·09*,†	2·05 ± 0·13†	0·98 ± 0·08*,†

* Significant difference from control group ($P < 0·05$).
† Significant difference from group treated only with amfonelic acid plus spiperone.

amfonelic acid (2·5 mg kg^{-1} s.c.). Amfonelic acid was a gift from Sterling Winthrop Research Institute, and spiperone was a gift from Janssen Pharmaceutica, Beerse, Belgium. Fluoxetine hydrochloride (synthesized in the Lilly Research Laboratories, Indianapolis, Indiana) was injected (10 mg kg^{-1} i.p.) 1 h before amfonelic acid. Rats were decapitated at the time specified. Brains were quickly removed and dissected; brain regions were frozen on dry ice and stored at −15 °C before analysis. Monoamines and metabolites were measured in brain regions by liquid chromatography with electrochemical detection (Fuller & Perry 1977; Perry & Fuller 1979). All data are shown as mean values ± standard errors for 5 rats per group. Statistical treatment of the data was by analysis of variance, and group mean values were compared by Tukey's honestly significant difference method based on the mean square error from the analysis of variance.

Results and discussion

Table 1 shows that the combination treatment with amfonelic acid and spiperone in rats decreased dopamine and 5-HT concentrations in the striatum but not in the hypothalamus. These findings are compatible with

Table 3. Lack of effect of fluoxetine pretreatment on the amfonelic acid/spiperone-induced changes in striatal concentrations of dopamine and its metabolites in rats.

	Dopamine and metabolites in striatum, nmol g^{-1}		
Treatment group	Dopamine	DOPAC	HVA
Control	80·7 ± 3·6	6·8 ± 0·3	3·3 ± 0·2
Amfonelic acid + spiperone	47·4 ± 3·8*	60·0 ± 11·8*	24·2 ± 3·6*
Amfonelic acid + spiperone + fluoxetine	39·1 ± 1·3*	70·7 ± 13·6*	23·9 ± 3·6*

* Significant difference from control group ($P < 0·05$).

spiperone. Table 3 shows that the decrease in striatal dopamine in rats treated with amfonelic acid and spiperone was accompanied by large increases in the dopamine metabolites, DOPAC and HVA, which were not antagonized by fluoxetine pretreatment.

The present findings confirm the observation of Waldmeier (1985) that striatal 5-HT is depleted acutely after the combined treatment with amfonelic acid and spiperone in rats and that a 5-HT uptake inhibitor prevents that depletion. Our findings extend those of Waldmeier (1985) by showing that the decrease in 5-HT is accompanied by an increase in the 5-HT metabolite, 5-HIAA. This increase and the increased ratio 5-HIAA/5-HT support the interpretation that 5-HT release is the mechanism for the decreased 5-HT concentration. Our findings show that uptake inhibition prevents the increased 5-HIAA/5-HT ratio. However, the increased ratio of DOPAC and HVA to dopamine was not prevented by the 5-HT uptake inhibitor, fluoxetine. These findings strengthen the interpretation by Waldmeier (1985) that increased dopamine release from dopaminergic terminals in the striatum after amfonelic acid and spiperone are given in combination, results in dopamine being accumulated by 5-HT nerve terminals, where it releases 5-HT from storage granules and exposes it to attack by monoamine oxidase.

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