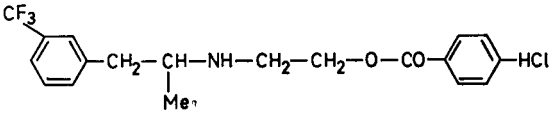
Anti-amphetamine activity of fenfluramine and S 992 in the isolated tail artery of the rat

Fenfluramine has been reported by several authors to reduce appetite in laboratory animals and in man in doses which do not influence the cardiovascular system (Franko, Houkomp & Ward, 1965; Le Douarec, Schmitt & Laubie, 1966; Colmore & Moore, 1966). S 992, a derivative of fenfluramine with the chemical structure I, elicits an anorexic activity of the same potency as that of fenfluramine, while the stimulant activity on the central nervous system is even less than that of fenfluramine (Le Douarec, personal communication). In a previous paper, fenfluramine was shown to decrease the toxicity of amphetamine in grouped mice while S 992 failed to show any protection in the same experimental conditions (Jespersen & Bonaccorsi, 1969). Because of the suggested interference between amphetamine and fenfluramine at the level of the receptor sites, we have studied the interaction in an isolated preparation, which is more suitable for the evaluation of this drug antagonism.



I

Tail arteries from 300 g rats were isolated in an organ bath and perfused at constant flow (8 ml/mm) with Krebs-Hucović solution saturated with 5% carbon dioxide in oxygen. The constrictor response of the artery was measured by recording the increase in perfusion pressure by means of a mercury manometer. Drugs were injected or infused through a rubber valve just before the artery.

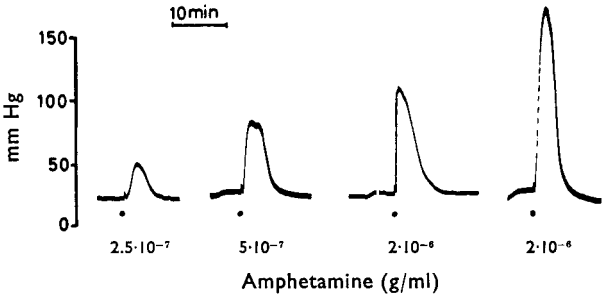


FIG. 1. The effect of tetrabenazine on the isolated tail artery of the rat after increasing amounts of amphetamine. At dots, 100 μg of tetrabenazine was injected. Amphetamine was perfused for 10 min before the tetrabenazine injection.

Reserpine and tetrabenazine elicit a long-lasting hypertensive effect when injected at a short interval after amphetamine (Bonaccorsi, 1968; Schmitt & Schmitt, 1969). The same kind of response can be reproduced in an isolated preparation. As can be seen from Fig. 1 the effect of tetrabenazine is dependent on the concentration of amphetamine. The onset of the constriction is slower compared with that of noradrenaline but it can reach high values. On the contrary tetrabenazine does not elicit any contraction when arteries are perfused with fenfluramine or S 992 at a concentration 10 or 100 times higher than that of amphetamine (Bizzi, Bonaccorsi &

others, 1968). To study the antagonism between amphetamine and fenfluramine, various concentrations of fenfluramine and S 992 were perfused for 10 min together with amphetamine. At the end of this period a constant dose of tetrabenazine was given which in control arteries, perfused with amphetamine, induced a nearly maximal contraction.

Table 1. *Inhibition by fenfluramine, S 992 or phentolamine (g/ml) of the constrictor response induced by amphetamine + tetrabenazine in the isolated tail artery of the rat*

	% inhibition after fenfluramine:				% inhibition after S 992:				% inhibition after phentolamine:	
	10^{-6}	$2{\cdot}5 \times 10^{-6}$	5×10^{-6}	$1{\cdot}25 \times 10^{-5}$	$2{\cdot}5 \times 10^{-8}$	5×10^{-8}	10^{-7}	$2{\cdot}5 \times 10^{-7}$	5×10^{-9}	10^{-8}
Amphetamine 10^{-6} g/ml + Tetrabenazine 100 µg	42	48	57	75	0	36	46	96	50	85
Noradrenaline 0·05 µg ..	0	0	15	40	0	10	20	60	35	50

Fenfluramine, S 992, or phentolamine were perfused for 15 min before adding amphetamine + tetrabenazine or noradrenaline.

As shown in Table 1 the antagonism is present for both substances tested but it is more evident for S 992, which, in fact, at a concentration of $2{\cdot}5 \times 10^{-7}$ g/ml abolished the contraction induced by amphetamine plus tetrabenazine, while fenfluramine was active only at the dose of 10^{-6} g/ml.

Since adrenolytics are potent inhibitors of the response induced by the combination amphetamine-tetrabenazine, we evaluated fenfluramine and S 992 for an adrenolytic effect. Fenfluramine hardly antagonized noradrenaline, while S 992 decreased the effect of noradrenaline at small concentrations. Its adrenolytic effect was promptly reversed by washing the preparation. Phentolamine, used as a control, was effective on the vasoconstrictor response induced by amphetamine, tetrabenazine or noradrenaline at a concentration at least 10 times lower than S 992.

The antagonism induced by S 992 is limited to the *in vitro* situation because *in vivo*, on the blood pressure, no adrenolytic activity can be shown.

Istituto di Ricerche Farmacologiche 'Mario Negri',
Via Eritrea, 62-20157 *Milan, Italy.*

J. JESPERSEN*
A. BONACCORSI

June 25, 1969

REFERENCES

BIZZI, A., BONACCORSI, A., JESPERSEN, S., JORI, A. & GARATTINI, S. (1969). In "*Amphetamine and related compounds*," Proc. International Symposium, Milan, 1969, in the press, New York: Raven Press.

BONACCORSI, A. (1968). *Europ. J. Pharmac.*, **3**, 97–105.

COLMORE, J. P. & MOORE, J. D. (1966). *J. new Drugs*, **6**, 123.

FRANKO, B. V., HOUKOMP, L. J. & WARD, J. W. (1965). *J. Pharm. Pharmac.*, **17**, 222–226.

JESPERSEN, S. & BONACCORSI, A. (1969). *Europ. J. Pharmac.* In the press.

LE DOUAREC, J. C., SCHMITT, H. & LAUBIE, M. (1966). *Archs int. Pharmacodyn. Thér.*, **161**, 206–232.

SCHMITT, H. & SCHMITT, H. (1969). In "*Amphetamine and related compounds*," Proc. International Symposium, Milan, 1969, in the press, New York: Raven Press.

* Visiting scientist from Department of Pharmacology A. Benzon, Copenhagen V, Denmark.