The interaction of desipramine and the 5-HT uptake inhibitors femoxetine and paroxetine with the acute hypotensive effect of guanethidine in conscious spontaneously hypertensive rats

ERLING N. PETERSEN, *A/S Ferrosan, Research Division, Sydmarken 5 DK 2860 Søborg, Denmark*

Many tricyclic antidepressant drugs have been shown to antagonize the antihypertensive effect of guanethidine (Leishman et al 1963; Mitchell et al 1967, 1970; Stafford & Fann 1977). The mechanism of action is presumably inhibition of neuronal noradrenaline (NA) uptake (Mitchell & Oates 1970). The selective 5HT uptake inhibitors femoxetine (FG 4963) and paroxetine (FG 7051) are both weak NA uptake inhibitors compared with the tricyclic antidepressants (Buus Lassen et al 1975a,b; Squires, Ferrosan internal report). Low doses of desipramine and high doses of paroxetine potentiate the heart rate response to NA in pithed rats (for method see Buus Lassen et al 1975b) probably as a result of NA uptake inhibition. Femoxetine has no influence on this NA response. Although structurally related, femoxetine and paroxetine may therefore interact differently with guanethidine.

Guanethidine is a weak hypotensive drug in Wistar rats. Therefore we used spontaneously hypertensive male rats (SHR) KYOI/NIH/MOL, 250–350 g prepared for direct recording of the blood pressure (b.p.) and injection of drugs according to Popovic & Popovic (1960). The rats received heparin 1 mg kg^{-1} i.v. initially, and later the tip of the 50 cm long catheter was kept free from clotting by infusion of 0·9% NaCl at a rate of 2 ml h^{-1} by means of a pressure reduction device, Intraflo CFS-03F (Sorenson Research Company, U.S.A.). A closely coiled spring 15 cm long was secured about the polyethylene lead 2 cm from the free end to prevent the rats biting through it. B.p. was continuously recorded on a Hewlett-Packard 7758 A recorder. The heart rate (HR) was calculated as the pulse rate.

The dosing started 2 h after the rats woke up from the short-lasting hexobarbitone sodium (100 mg kg^{-1} i.p.) anaesthesia. In the reversion experiments guanethidine 5 mg kg^{-1} i.v. was injected at time 0 and followed 15 and 30 min later by 1 and 5 mg kg^{-1} i.v. of femoxetine, paroxetine or desipramine. In the prevention experiments the drugs were given 15 min before guanethidine 5 mg kg^{-1} i.v. given at time 0. Statistical evaluation was using Student's *t*-test, where all values were compared with the value at time 0. All values are the mean of 5 experiments and their standard deviations are less than 10% (omitted in Fig. 1).

The groups of conscious SHR used in these experiments did not vary much in their mean basal b.p. values, while the HR's showed considerably more variation and were from 320–420 beats min^{-1}. The hypotensive effect of guanethidine in the control experiments was about 40 mm Hg systolic and about 60 mm Hg diastolic both developing within the first minutes after the injection. The b.p.'s were still significantly lowered at 60 min. The HR increased rapidly to about 490 beats min^{-1}, but returned to the basal value 15 min later.

The three test substances given cumulatively, 1 and 5 mg kg^{-1} i.v., did not reverse the guanethidine response. Desipramine 1 mg kg^{-1} i.v. totally prevented the hypotensive effect of guanethidine. Paroxetine 5 mg kg^{-1} i.v. prevented the guanethidine response to some degree and femoxetine 5 mg kg^{-1} i.v. prevented it to a somewhat lesser degree than paroxetine. After paroxetine or femoxetine pretreatment guanethidine still produced a significant hypotension, except of the diastolic b.p. with paroxetine. All three drugs decreased the HR response to guanethidine, desipramine to the highest degree.

It seems to be more difficult to acutely reverse an established hypotensive effect of guanethidine than to prevent it (Ober & Wang 1973). This fits very well with the proposed mechanism of action of guanethidine. Guanethidine must gain access to the intraneuronal medium to produce its blockade of neuronal release of NA (Mitchell & Oates 1970). As guanethidine is taken up by the NA uptake mechanism into the neuron, drugs which inhibit this uptake also will prevent the effect of guanethidine (Mitchell & Oates 1970). The uptake inhibition has thus to be present at the time of guanethidine administration to produce an effect in acute experiments (Stone et al 1964). However, during chronic treatment, as in the clinical situation, NA uptake inhibitors may slowly reduce the effect of guanethidine as released guanethidine presumably cannot be replaced by an equal amount of guanethidine taken up by the neuron.

These experiments with spontaneously hypertensive rats have demonstrated the clearcut interaction between guanethidine and desipramine. The two selective 5-HT uptake inhibitors both have some effect on the hypotensive effect of guanethidine which shows that their selectivities are relative, in accordance with the in vitro experiments (Buus Lassen 1975a; Squires, Ferrosan internal report) and the in vivo experiments on pithed rats (the doses doubling the integrated HR response to Na in pithed rats were, mg kg^{-1}, desipramine 0·01, paroxetine 1·0, femoxetine $> 5·0$), paroxetine being stronger uptake inhibitor for both 5-HT and NA. Although femoxetine and paroxetine both antagonize guanethidine, their effects are only partial at the high dose 5 mg kg^{-1} i.v. and therefore presumably of no

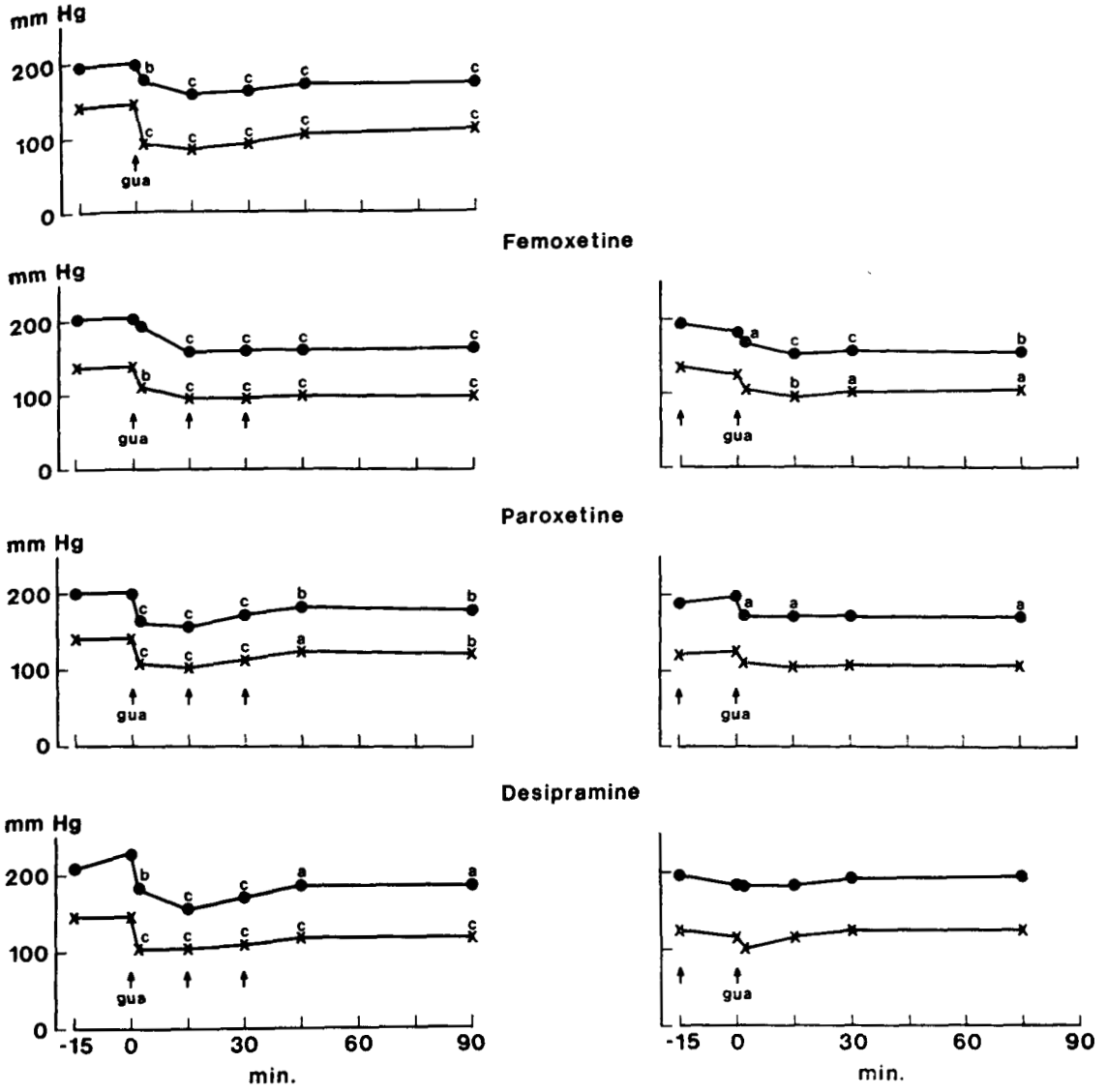

FIG. 1. The heart rate and the systolic (●—●) and diastolic (×—×) blood pressure responses obtained in conscious SHR. In the left column guanethidine 5 mg kg^{-1} i.v. (gua) is either followed by femoxetine, paroxetine or desipramine all 1 and 5 mg kg^{-1} i.v. given cumulatively at the arrows. At the top a control response to guanethidine 5 mg kg^{-1} is shown.

In the right column guanethidine 5 mg kg^{-1} i.v. is preceded by femoxetine 5 mg kg^{-1} i.v., by paroxetine 5 mg kg^{-1} i.v. or by desipramine 1 mg kg^{-1} i.v. at the arrow. All values are the mean of 5 experiments and their standard deviations are less than 10% of the mean value and for clearness omitted. All values are compared with the value at time 0 by Student's *t*-test (a. $P \leq 0.05$ b. $P \leq 0.01$ c. $P < 0.001$).

clinical significance. These 5-HT uptake inhibitors may be alternatives to the NA uptake-inhibiting antidepressant drugs for the depressed patient treated for severe hypertension with guanethidine and guanethidine-like antihypertensive drugs.

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REFERENCES

Buus Lassen, J., Squires, R. F., Christensen, J. A., Molander, L. (1975a) Psychopharmacologia (Berlin) 42: 21–26

Buus Lassen, J., Petersen, E., Kjellberg, B., Olsson, S. O. (1975b) Eur. J. Pharmacol. 32: 108–115

Leishman, A. W. D., Matthews, H. L., Smith, A. J. (1963) Lancet 1: 112

Mitchell, J. R., Oates, J. A. (1970) J. Pharmacol. Exp. Ther. 172: 100–107

Mitchell, J. R., Arias, L., Oates, J. A. (1967) J. Am. Med. Ass. 202: 149–152

Mitchell, J. R., Cavanaugh, J. H., Arias, L., Oates, J. A. (1970) J. Clin. Invest. 49: 1596–1604

Ober, K. F., Wang, R. I. H. (1973) Clin. Pharm. Ther. 14: 190–95

Popovic, V., Popovic, P. (1960) J. Appl. Physiol. 15: 727–8

Stone, C. A., Porter, C. C., Stavorski, J. M., Ludden, C. T., Totaro, J. A. (1964) J. Pharm. Exp. Ther. 144: 196–204

Stafford, J. R., Fann, W. E. (1977) Drugs 13: 57–64

Adrenocortical stimulation and the anti-inflammatory actions of salicylates

J. R. WALKER*, M. J. H. SMITH, *Biochemical Pharmacology Research Unit, Department of Chemical Pathology King's College Hospital Medical School, Denmark Hill, London, SE5 8RX, U.K.*

The mechanism by which salicylates (and other acidic non-steroidal anti-inflammatory drugs) exert their anti-inflammatory activity has been a matter of some controversy for a number of years. Evidence accumulated over the last decade has led to a hypothesis that their mode of action resides in the ability of the drugs to inhibit the production of biologically active lipids from arachidonic acid by inhibiting prostaglandin cyclo-oxygenase (Ferreira & Vane 1979; Vane 1978). Whilst this effect is not disputed, there is now available a substantial literature which would argue that other anti-inflammatory actions of these drugs, particularly those directed against leucocyte accumulation in inflammatory exudates, are unrelated to their effects on prostaglandin cyclo-oxygenase (Walker et al 1976; Glenn et al 1977; Atkinson & Leach 1978; Smith 1978).

It is therefore pertinent to examine other actions of these drugs which may account for their effects on leucocyte accumulation at inflammatory sites. One possibility is stimulation of the adrenal cortex, a suggestion which originally arose because of the efficacy of steroids in rheumatic diseases (Hench 1950). While the evidence for this postulate, at least for anti-inflammatory doses of aspirin, is weak (Smith 1966), it has nevertheless recently been proposed that leucocyte accumulation into pleural exudates may be inhibited by a systemic action of aspirin via stimulation of the adrenal cortex (Vinegar et al 1978).

The experiments reported here were designed to explore the possibility that the inhibitory effects of aspirin, and its immediate metabolite, salicylic acid, on leucocyte accumulation and prostaglandin-like activity in subdermally implanted sponge exudates may be due to stimulation of the adrenal cortex.

The sponge implantation method, determination of prostaglandin-like activity and leucocyte accumulation in 9 h sponge exudates have been described in detail elsewhere (Ford-Hutchinson et al 1978). Bilateral adrenalectomy was performed by standard methods, the animals being maintained on 0·9% NaCl and used 8 days after the operation. Aspirin (acetylsalicylic acid) and salicylic acid (BDH, Poole, Dorset) were given orally as a suspension in Tween 80, or locally, distributed in the solid form throughout dry sponges (Walker et al 1976).

The results obtained after systemic administration of the drugs to normal and bilaterally adrenalectomized animals are shown in Tables 1 and 2. It is clear that bilateral adrenalectomy enhances two important aspects of the inflammatory reaction, the formation of prostaglandin-like activity, which has been increased approximately sixfold, and leucocyte accumulation in the exudate, which has doubled. The results of other experiments showed that sham-operated animals did not differ significantly from normal rats with respect both to the content of prostaglandin-like activity and leucocyte accumulation in the exudates and the effects of aspirin on these parameters. While the absolute values for both parameters are higher after treatment with either aspirin or salicylic acid in the adrenalectomized animals compared with the control groups, the mean percentage inhibition afforded by the drugs at the doses used are similar. Local application of aspirin and salicylic acid gave a predictable result; aspirin (0·5 mg) inhibited the production of prostaglandin-like material by 84% without affecting leucocyte accumulation (number of rats = 10), and salicylic acid (0·5 mg)

Table 1. Effects of oral administration of aspirin and salicylic acid on the accumulation of prostaglandin-like activity and leucocytes in 9 h sponge exudates in normal rats.

Drug	Dose mg kg^{-1}	PGE_2 equiv. (ng ml^{-1} exudate)	% inhibition	Total white cells ($\times 10^6$ ml^{-1} exudate)	% inhibition
Control (10)	—	10·3 ± 1·3	—	7·67 ± 0·50	—
Aspirin (5)	50	4·1 ± 0·1	59·8*	5·27 ± 0·35	31·3*
Aspirin (10)	200	2·1 ± 0·2	80·1*	3·93 ± 0·41	49·3*
Salicylic acid (5)	50	2·6 ± 0·3	75·2*	5·65 ± 0·25	26·0†
Salicylic acid (5)	200	2·0 ± 0·3	81·0*	4·39 ± 0·35	42·7*

Figures in parenthesis indicate the number of animals per group. Results expressed as mean ± s.e.m.
† $P < 0·05$, * $P < 0·005$.

* Correspondence and present address: Department of Allergy, Lilly Research Centre Ltd, Erl Wood Manor, Windlesham, Surrey, U.K.