Cardiovascular effects of baclofen in the rat

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One of the lipophilic derivatives of γ-aminobutyric acid (GABA) that penetrates the blood brain barrier better than the parent compound is β-(*p*-chlorophenyl)-GABA (baclofen) (Faigle & Keberle 1972). This agent has proved useful in alleviation of spasticity in the man (Birkmayer 1972), and has also been used for direct or indirect activation of GABA mechanisms. The finding that another GABA analogue, γ-hydroxybutyric acid (GHBA), causes a sustained hypertension in the rat (Gomes et al 1976), prompted us to study the cardiovascular effects of baclofen. In the man baclofen has been reported to lower blood pressure (Pinto et al 1972) as also seems to be the case for anaesthetized animals (Suzuki & Murayama 1975).

Male Sprague-Dawley rats, 200–270 g, were used. Mean arterial blood pressure was recorded in conscious unrestrained animals through in-dwelling catheters (a. carotis) connected to Statham P23Dc pressure transducers writing on a Grass polygraph (Trolin 1975). Intravenous (i.v.) catheters were implanted into the jugular vein as described by Trolin (1975) and intracerebroventricular catheters (4th ventricle) were implanted as described by Gomes et al (submitted for publication). In one group of rats the spinal cord was transected at the C7 level according to Gomes (1978).

The drugs used were β-(*p*-chlorophenyl)-GABA (baclofen), DL-α-methyl-*p*-tyrosine methylester (AMPT), DL-α-methylmetatyrosine (AMMT), pentobarbitone (sodium form), phenoxybenzamine, hexamethonium, spiroperidol, picrotoxin, bicuculline, atropine, physostigmine, 3-mercaptopropionic acid (3-MPA) and aminooxyacetic acid (AOAA). Drugs were given i.p. at a volume of 10 ml kg^{-1}, i.v. at a volume of 2 ml kg^{-1} and i.c.v. at a volume of 10 μl. Significances were calculated using an analysis of variance with one or two independent criteria for classification, followed by a *t*-test.

Intraperitoneal baclofen (5 mg kg^{-1}) within 10–20 min caused a sustained hypertension and tachycardia (Fig. 1). The hypertension was reversed into a significant hypotension ($P < 0.05$, 15–120 min, n = 6) by acute spinalization (2 h). This suggests a supraspinal site of action for the circulatory response to baclofen and this is supported by the observation that i.c.v. baclofen in doses above 0·125 μg (n = 21) elicited hypertension and tachycardia of the same magnitude and duration as seen after i.p. baclofen. The cardiovascular effects of baclofen (5 mg kg^{-1} i.p.) were also blocked by hexamethonium (15 mg kg^{-1} i.p., 30 min after baclofen, n = 5) and phenoxybenzamine pretreatment (15 mg kg^{-1} i.p., 12 h and 5 mg kg i.p., 3 h before baclofen) and were significantly attenuated ($P < 0.005$ 15–120 min for blood pressure, n = 8) following catecholamine depletion by means of AMMT (400 mg kg^{-1} i.p., 24 and 12 h before baclofen) in combination with catecholamine synthesis inhibition by means of AMPT (250 mg kg^{-1} i.p., 3 h before baclofen). Thus it would seem that an intact noradrenergic system is important for the cardiovascular actions of baclofen.

GABA mechanisms have interesting connections with acetylcholine and dopamine (Iversen 1978). The circulatory response to baclofen (5 mg kg^{-1} i.p., 30 min) was not influenced by atropine (10 mg kg^{-1} i.p., n = 5), physostigmine (0·1 mg kg^{-1} i.v., n = 5), spiroperidol (0·25 mg kg^{-1} i.p., n = 5), picrotoxin (2 mg kg^{-1} i.p., n = 4) or bicuculline (4 mg kg^{-1} i.p., n = 5). Apomorphine (3 mg kg^{-1} i.p., n = 5) caused a shortlasting lowering of blood pressure which was not different from that seen in controls (apomorphine alone, n = 7). Pretreatment with agents influencing GABA metabolism, i.e. 3-MPA which inhibits glutamic acid decarboxylase (25 mg kg^{-1} i.p., 5 min before baclofen, n = 5) and AOAA which inhibits GABA-transaminase (30 mg kg^{-1} i.p., 5 h before baclofen, n = 5), did not influence the circulatory effects of baclofen, 2·5 mg kg^{-1} i.p. Pentobarbitone pretreatment (60 mg kg^{-1} i.p., 30 min before baclofen) completely prevented the cardiovascular actions of baclofen, 5 mg kg^{-1} i.p.

It seems that baclofen in the rat causes hypertension and tachycardia by a central mechanism of action in which the sympathetic system is involved. There were no indications for an involvement of dopaminergic or cholinergic mechanisms. In addition, the circulatory

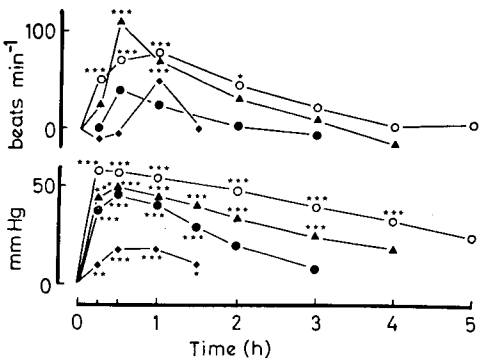

FIG. 1. Cardiovascular effects of intraperitoneal baclofen. The values are changes in mean arterial blood pressure (mm Hg, lower ordinate) and heart frequency (beats min^{-1}, upper ordinate) from basal level (time 0). Abscissa: time (h). Basal levels are indicated within brackets as: b.p. mm Hg/HR beats min^{-1}. ○ 10 mg kg^{-1}, (113/361), n = 5. ▲ 5 mg kg^{-1}, (110/379), n = 7. ● 2·5 mg kg^{-1}, (113/358), n = 5. ◆ 1·25 mg kg^{-1}, (122/354), n = 6. * indicate significant differences from basal level. * $P < 0.05$, ** $P < 0.025$, *** $P < 0.005$

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effects of baclofen did not seem GABA mediated which is in support of several reports questioning the specificity of baclofen as a GABA agonist (for ref. see Mao & Costa 1978).

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LETTER TO THE EDITOR

A cautionary note on the use of ordered powder mixtures in pharmaceutical dosage forms

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Ordered powder mixtures (Hersey 1975) have become an acceptable method of preparing a highly homogenous powder mixture (Yip & Hersey 1976, 1977; Crooks & Ho 1976; Rees 1975; Yeung & Hersey 1979). Such mixtures appear to have wide application in the preparation of dosage forms containing relatively small doses of highly potent drugs. In this situation, the drug particles would be finely divided and highly cohesive, allowing them to adhere to a more coarse carrier particle.

We wish to caution those pharmaceutical formulators, who having prepared a highly homogenous ordered powder mixture, wish to use this mixture in the development of a dosage form. The addition of a third component may, if it preferentially adheres to the carrier particles, displace the original drug particles from their adhesion sites. The situation is exactly anomalous to that occurring at adsorption sites or in protein-binding problems, where a third component is preferentially absorbed.

An alternative explanation is that the third component may interfere with the adhesion of the drug onto the carrier particles, effectively stripping them from that substrate. In this case the third component itself is not bound to the carrier articles and does not replace the drug particles it has stripped from the carrier.

An ordered powder mixture containing 0·2% salicylic acid of particle size 3·4 μm onto carrier particles of 425–620 μm sucrose particles was produced after 5 h in the Revolvo-cube mixer.

The cohesiveness of the salicylic acid is demonstrated by the fact that the mix was sifted at 106 μm for 120 min, during which period only 0·45% of the salicylic acid passed through the screen.

Subsequently 4% of the magnesium stearate was added to the cube mixer and mixed for a further 5 h. Again the mix was sifted at 106 μm for 120 min. Under these conditions, 7·09% of the salicylic acid passed through the screen. This figure was further increased to 10·89% after a further 3 h sifting, indicating that the magnesium stearate is seriously affecting the adhesion of salicylic acid particles to the sucrose carrier. Since magnesium stearate itself is also being removed from the mix through the screen to the extent of 26·8% after 5 h sifting, it would appear that the magnesium stearate is stripping the salicylic acid particles from the sucrose carrier rather than replacing it as a preferential adhesive.

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